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THE DIAPHRAGM: SOME REFLECTIONS ON ITS FUNCTION AND ITS DISEASES[1]

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Mrs. A. S., aged 69 years, complained of gas and distress of 12 years duration. For one year her symptoms had increased in severity. She had always had a voracious appetite and had been overweight, but in recent years her appetite had diminished and she lost weight. For 10 years she complained of heartburn one or two hours after meals, usually relieved by baking soda. The intense burning pain was located behind the sternum, and on occasion it extended upward into the neck. At times the discomfort radiated into the back, the right shoulder, or the left arm. One physician told her that she had angina pectoris and treated her with nitroglycerine.

Beside coming on one or two hours after a meal, the pain became noticeable when the patient exerted herself by stooping forward, as in lifting or straining. It awakened her in the middle of the night, especially if she was sleeping on her back, and she would seek relief by sitting upright, getting out of bed, and taking sips of water, milk or sodium bicarbonate. When she swallowed food, she was conscious of its passing down the esophagus. There was a feeling of soreness, and the food sometimes seemed to lodge toward the lower end of the sternum, causing pain which was relieved when the food passed into the stomach. When she bent forward after a meal, food or some fluid rose into her throat and had to be swallowed again.

All the symptoms had become worse during the past year. The patient complained bitterly of eructation of gas and excess flatus, and her family said that for belching "Grandma takes the prize." For over a year there had been a steady decrease in appetite until she was reduced to tea and toast. She complained of being run down, tired, weak, high-strung, irritable, nervous, and anxious. She was afraid to eat. She had lost 25 pounds in weight.

The patient had been told by another physician that she had gall bladder disease, but a Graham-Cole test showed normal filling of the gall bladder and no evidence of stones. She had tried all the antacids, proprietary and nonproprietary. She had been told that she had nervous indigestion following the change of life and had received injections of hormones and vitamins. She could not sleep. She could not eat. She had palpitations at night.

[1] Lecture II of the twenty-second course of lectures under the William Sydney Thayer and Susan Read Thayer Lectureship in Clinical Medicine. Delivered at The Johns Hopkins Hospital April 27, 1956.

The examination disclosed an elderly woman, alert but anxious and tense, who belched large quantities of gas as one talked to her. She showed evidence of loss of weight. The abdominal muscles were lax, the linea alba was open, and there was a small umbilical hernia. All other examinations were negative except for the x-ray examination of the esophagus, stomach, and diaphragm.

It then became clear that the patient's symptoms were due to esophagitis from the reflux of gastric contents into the esophagus. There was a gliding hernia of the stomach through the esophageal hiatus of the diaphragm into the posterior mediastinum. When the patient was tilted in the head-down position, the herniated part of the stomach was distended with barium and easily demonstrated. When the stomach was filled with barium and she bent forward, the barium flowed back into the esophagus and pharynx.

This story, with a few minor variations, is highly characteristic of hiatal esophageal hernia of the gliding type, one of the commonest disorders of the diaphragm. The symptoms are due to reflux of gastric contents into the esophagus with esophagitis.

STRUCTURE AND FUNCTIONS

Hiatal hernias serve to direct attention to one of the most important muscles of the human body. The diaphragm is a muscle of inspiration and plays a tremendous role in maintaining both normal respiration and circulation. It plays a great part in maintaining the normal pressure relationship between the thorax and abdomen, and in the movement of the organs of the thorax and abdomen during respiration. The diaphragm serves as the floor of the thorax and the roof of the abdominal cavity. It is raised and lowered with respiration and acts in many respects like a movable piston.

Normally the diaphragm moves regularly from birth until death, and because it separates the thorax from the abdomen, it is functionally associated with nearly all of the organs with which it is in contact. Of all the striped muscles, it is probably the most affected by disease processes. Characteristically, it has the greatest power of all striped muscles to remove oxygen from its environment. It has the greatest resistance to physiologic fatigue and it has superior ability to respond to various stimuli (Meleney-Lee) (1).

The diaphragm has a rich blood and nerve supply and an active lymphatic system. It is supported by the structures of the thorax, both central and costal, and by the abdominal contents and abdominal wall. It is capable of powerful movements. It is important in coughing, eructation, defecation, urination, sneezing and yawning, singing and speaking. In brief, it is essential for all respiratory effort and function.

A number of important structures pass from the thorax through the diaphragm to the abdominal cavity: the esophagus, the aorta, and the inferior vena cava. The relations of these structures to the diaphragm and the dis-

turbances that may arise in the areas of the roadway need to be understood. There are certain weak spots that need to be recognized and studied and, as in all other muscles, disorders of structure are followed by disorders of function.

POSITION AND MOVEMENT

The importance of the normal movement of the diaphragm has been emphasized in recent years due to the intensification of studies of pulmonary function in patients with emphysema and other forms of primary lung disease. Also, the study of diaphragmatic paralysis in poliomyelitis has promoted the development of new techniques for movement of the diaphragm such as the phrenic stimulation of Sarnoff and respirators for positive and negative pressure breathing. Further, the extension of pneumonectomy and thoracoplasty has stimulated interest in diaphragmatic movement.

Several years ago Dr. Henry Thomas, Jr. (2) directed attention to the adjustments that were made in breathing following pneumonectomy, thus stimulating renewed activity in respiratory function. Dr. Thomas described paradoxical movement of the diaphragm following pneumonectomy when a small bronchofistula existed with a pneumothorax, and a normal but decreased up-and-down movement of the diaphragm with a shift of the mediastinum when no fistula existed.

So, in all studies of pulmonary function, it is important to take into account the position and movement of the diaphragm as well as of the chest wall, because the diaphragm is the most powerful muscle of inspiration, and interference with its movement or function throws greater work on the other muscles of respiration.

While there are many primary diseases of the diaphragm, there are many other diseases that are secondary to the spread of diseases from neighboring organs. Both primary and secondary diseases cause functional disturbances. In this lecture, I propose discussing some congenital and acquired defects of the diaphragm, the effects of the diaphragm on respiration and circulation, some disturbances caused by impairment of movement of the diaphragm, and finally, direct attention to some of its uncommon diseases. To understand some of the defects of diaphragmatic function it is necessary to review some of its anatomical features.

EMBRYOLOGY

The early studies of Mall (3) and Keith (4) have provided information concerning the development of the diaphragm. Maldevelopment or defects in this muscle appearing after birth or in adult life or old age, tend to occur in certain areas (Fig. 1). The diaphragm is made up of a dorsal and a ventrolateral segment, and they fuse in the central tendon. The central tendon is formed from the septum transversum, in the formation of which the dorsal and ventral

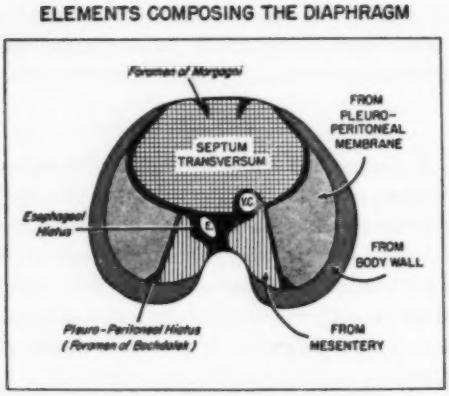

FIG. 1. Elements composing the diaphragm. Note that congenital hernias, as well as acquired and traumatic hernias, are likely to occur at the foramina or at the line of fusion between the elements that make up the diaphragm in its development.

mesentery of the foregut are included. The structures developed in these mesenterics, the aorta, esophagus, azygos veins, thoracic duct, vagus nerves and inferior vena cava, perforated the median or central part of the diaphragm.

The dorsal segment of the diaphragm is made up of the muscular fibers which arise from the spine and arcuate ligaments. The ventrolateral part is derived from the ventral longitudinal muscle sheets, which give rise to the rectus abdominis on each side. Posteriorly, between the muscle fibers which rise from the ribs and the sternum (the ventrolateral part of the diaphragm) and those rising from the spine and arcuate ligaments, are the pleuroperitoneal openings. These openings close during embryonic life, but the extent to which this closure takes place is extremely variable. Wide openings give rise to hernias, which are more common on the left side than the right, because the liver helps to close the apertures on the right side by its upgrowth within the septum transversum. Also, when a pleuroperitoneal opening is covered only by peritoneum and pleura, infections may transgress from the pleura to the retroperitoneal space or in the opposite direction. These are referred to as reciprocal infections.

The normal diaphragm after its development and fusion is a true digastric muscle, made up of two segments, a spinal or dorsal and a costal or ventral. The spinal segment, consisting of crural and arcuate fibers, takes its origin from the upper three lumbar vertebrae and from the arcuate ligamentous thickenings of the sheathes of the psoas and quadratus lumborum muscles.

The spinal fibers expand as they ascend, terminating as fibrous strands in the central tendon, from which most of the costal segments diversify. The costal fibers spread as they descend in front of their insertion in the abdominal and ventral ends of the lower six ribs, but as a rule there is no insertion to the

twelfth rib. The fibrous interval between the spinal and costal fibers is the site of communication between the pleural and peritoneal cavities.

The costal segment of the diaphragm can be divided functionally into two parts: the anteromedial portion, which is made up of the fibers extending from the central tendon to the attachments of the 6th, 7th and 8th ribs anteriorly; and the posterior segment, which fuses through the central tendon with the strong fibers attached to the 9th, 10th and 11th ribs. The arrangement of these muscle fibers is important because the contraction of the spinal and posterior segment of the diaphragm is much more powerful than that of the anteromedial segment. This unequal contraction accounts for the changes in contour in the normal diaphragm known as the anteromedial bulge and for pseudo-paradoxical movement of the diaphragm, which I shall discuss presently.

From what has been said so far, it is plain that the diaphragm is anchored to the spine, the lower six ribs, and the structures that pass through it. This shelf or dome between the chest and abdomen has three principle supports: abdominal, thoracic, and costal. These supports are important because the diaphragm is in regular motion and requires support in all positions.

TYPES OF DIAPHRAGMATIC HERNIA

At the outset, I described the history of a patient with an esophageal hiatal hernia. A more detailed discussion of the types of diaphragmatic hernia is now in order. While there are many elaborate classifications such as congenital and acquired, true and false, traumatic and nontraumatic, it is plain that these communications between the thorax and abdomen tend to occur at certain points in the diaphragm (Figs. 2, 3, 4).

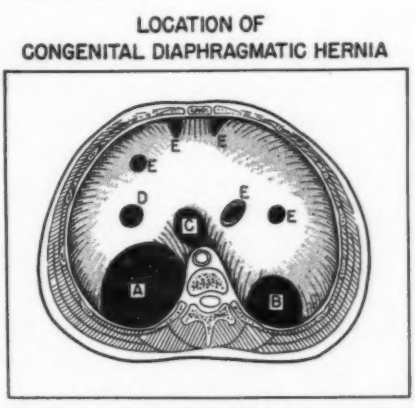

FIG. 2. Locations of congenital diaphragmatic hernias. A—Left side pleuroperitoneal hiatus. B—Right side pleuroperitoneal hiatus. C—Esophageal hiatus. D—Central tendon right side. E—Infrequent sites for congenital hernias. Inferior vena cava orifice, central tendon right side, parasternal areas and junction of central tendon right side and muscular attachments.

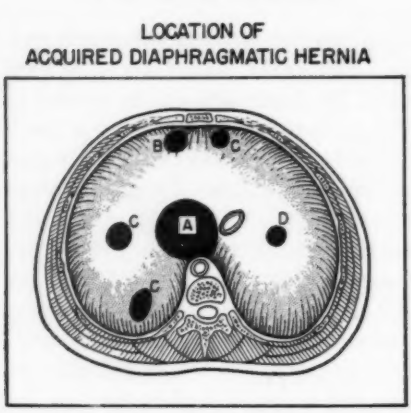

FIG. 3. Locations of acquired diaphragmatic hernias in order of frequency. A—Esophageal hiatus. B—Left parasternal area. C—Right parasternal area, central tendon and posterior pleuroperitoneal hiatus left side. D—Central tendon right side.

It can be seen from the illustrations that the commonest sites for congenital hernias are the peritoneopleural openings, and they are more common on the left side than on the right. In order of frequency, they are observed at the esophageal hiatus, the central tendon, and in the parasternal region. When hernias appear after birth they are encountered most often at the esophageal orifice, the parasternal area, the central tendon, and the posterior and anterior segments, in that order. Hernias that follow trauma usually occur on the left side at the central tendons, posteriorly and anteriorly, rarely on the right side.

Esophageal hiatal hernia

The esophageal hiatal hernias are the commonest acquired hernias of the diaphragm. They are of four anatomical types: 1) the sliding or gliding type, the commonest, 2) the paraesophageal, 3) the combined type, and 4) the short esophagus. There have been numerous excellent studies of these types of hernia. Since they increase in frequency with age, since physicians are seeing more elderly people, and since many hernias can be repaired with success, the problem of their control is becoming more and more important.

The esophagus is attached to the cricopharyngeal muscle of the pharynx above the diaphragm and to the cardia of the stomach below it. At the cardia, the esophagus bends forward and to the left at an acute angle. It is freely movable in the chest from side to side and is bound loosely to the mesentery of the spine by post-reflection of the mediastinal pleura.

The esophagus is anchored to the diaphragm at the hiatus as follows: The hiatus is formed by a split in the muscle fibers arising from the right crus of the diaphragm, lightly reinforced by fibers from the left. That is to say, the fibers from the right crus split and continue on each side of the esophagus and

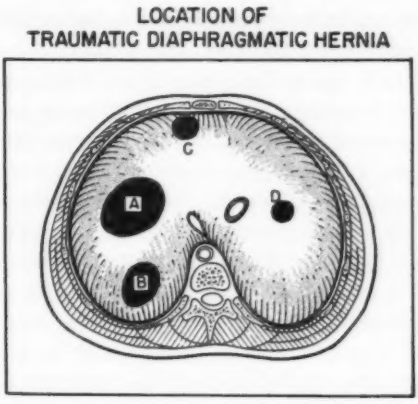

FIG. 4. Common locations of traumatic diaphragmatic hernias. A—Central tendon left side. B—Posterior segment of diaphragm left side. C—Parasternal region left side. D—Central tendon right side.

decussate with one another to form a stoutly reinforced raphe in the central tendon. Behind the esophagus there is less support because it is here that the muscle splits and divides for the hiatus. Thus, the esophagus is lassoed by the right crus of the diaphragm and attached to the spine below.

On the under surface of the hiatus, the bare area of the stomach, the retroperitoneal tissue is in continuity with that of the crural canal. Fat accumulates here between the stomach and esophagus to form what Anders calls the "subdiaphragmatic fat ring." This wedge of fat surrounds the hiatus and forms a barrier for increased intra-abdominal pressure. On the upper surface of the hiatus there are lymph vessels and the paracardiac lymph nodes and connective tissue.

The main anchor of the diaphragm to the esophagus is the phrenicoelastic ligament or membrane. It is well developed in some people, but when hernias are present there is often evidence that this ligament is rudimentary or has atrophied considerably. It arises from the deep fascia and the pillars of the diaphragm and surrounds the esophagus at the hiatus, where it divides into two segments, the ascending and the descending. The ascending part extends upward into the thickened portion of the esophageal wall above the diaphragm, where these elastic fibers enter the two muscular layers of the wall and become anchored there, especially in the circular layer. The elastic fibers of the descending part of the membrane enmesh the fat globules between the diaphragm and the stomach and pass into the musculature of the stomach, where they become anchored. The membrane is separated from the diaphragmatic esophagus in the middle and the peritoneal reflection below by the gastric vessels where they emerge from the retroperitoneum to enter the stomach and esophagus.

The relation of the cardia to the diaphragm is dependent partly upon muscular action and partly upon ligament attachment. The peritoneum of the stomach is reflected onto the under aspect of the diaphragm, and it is closely applied to both these structures, where its reflection forms a sort of ligament.

The abdominal portion of the esophagus is very short, usually not more than 2 cm. in length. It lies in the epigastric region of the abdomen. Anteriorly is the left lobe of the liver; posteriorly the decussating fibers of the crura of the diaphragm and the left inferior phrenic artery. To the right is the caudate lobe of the liver, and to the left, the left lobe of the liver and the fundus of the stomach. In the canal of the crura is a wedge-shaped fat pad or ring.

As the esophagus passes through the diaphragmatic hiatus, the right vagus lies behind and the left vagus anteriorly. In hernias of the gliding type, the peritoneal attachments of the cardiac end of the stomach, the gastric arteries and the phrenicoesophageal membrane are stretched.

Gliding hiatal hernia

In the gliding type of hernia, no hernial sac exists but there is general weakness of the diaphragm and its supports, as well as stretching and weakening of the ligaments at the cardia. In some cases the subdiaphragmatic fat ring atrophies after the hiatus which it surrounds has widened it. As the diaphragm falls, due to lack of support, and the peritoneal attachments are stretched, the acute angle between the stomach and esophagus disappears. At first the esophagus may elongate, but later, due to its elasticity and the intraperitoneal pressure, the cardia slips into the posterior mediastinum, taking the elongated ligament and its peritoneal reflection with it.

The stomach then hangs like a bell from the esophagus. The highly elastic esophagus recoils and retracts and appears shorter than normal, but in fact it is usually not shortened since it can be pulled back to position, unless there is so much scar formation from esophagitis that it has lost its contractile power.

To understand the sequence of events and the factors involved in this type of hernia, it is necessary to examine the supports and mobility of the diaphragm, the attachments of the esophagus to the diaphragm and to the stomach, and the posterior mediastinal mesentery and pharynx.

It has been remarked that in a sliding hernia the esophagus and the cardia of the stomach are pulled into the mediastinum, and this is assisted by anything that increases intra-abdominal pressure. The esophagus enters the stomach above the diaphragm.

Parahiatal hernia

There is another type of hernia which is much less common. The symptoms are different and the disease at the esophageal hiatus is different. This is the congenital or parahiatal hernia. It is sometimes associated with a sliding hernia, and it may not appear until late in life.

In the normal development of the stomach, it prolapses from the thoracic region as a part of the foregut, into the peritoneum, leaving the cardia bare on its posterior surface. A small protrusion of the peritoneum may be left in the mediastinum, in front of the esophagus. This preformed hernial sac may remain empty throughout life, or a part of the anterior surface of the stomach may project into it at any age from birth to old age. The hernia can fill by rolling up the anterior part of the stomach and so produces the upside-down stomach with a peritoneal sac. The colon may even be pulled into the thorax by this gastrocolic membrane. In this type of hernia the esophagus enters the stomach *below* the diaphragm and at an acute angle. The dilated stomach often compresses the esophagus between the spine and the pericardium. Regurgitation of stomach contents does not occur.

These patients complain of fullness after meals, palpitation, and shortness of breath. Some develop gastric ulcers at the point of constriction, and 5 to 6 per cent of them may bleed or perforate, or they may develop volvulus of the stomach or obstruction of the colon.

Combined sliding and parahiatal hernia

In a few patients there is a combined type of hernia in which the esophagus is elevated and there is a true hernia enclosed in a sac, containing a bit of the stomach. The paraesophageal hernia is often separated from the hiatus by a thin strand of tissue.

In summary, hiatal hernias tend to occur in elderly people and cause reflux esophagitis. They are especially frequent in people who are overweight or in those who have been considerably overweight before their symptoms occurred. There is a widened hiatal ring with atrophy or weakening of the diaphragmatic supports, a widening of the crus of the diaphragm, a loss of elasticity and stretching of the phrenicoesophageal ligament and loss of elasticity of structures of the peritoneal and gastric attachments of the stomach. The esophagus contracts and the gastric vessels lengthen. The abdominal walls are often weak and the descent of the diaphragm is defective. The pinchcock effect fails so that regurgitation is common. Any increase in the intra-abdominal pressure forces the cardiac end of the stomach into mediastinum.

When the supports of the diaphragm weaken, the hiatal ring widens, the diaphragm falls, and the esophagus meets the demand by elongating. The esophagus being very elastic, its abdominal termination is drawn within the thorax. Atrophy of the left lobe of the liver, atrophy of the fat pad, and increased intra-abdominal pressure are important contributing factors.

DIAPHRAGM SUPPORTS

We have seen that the diaphragm is sustained in its position and movement by three main supports: abdominal, thoracic, and costal, all of which are required for normal and coordinated function. A partial collapse of one is fol-

lowed by a corresponding failure of the other. The *abdominal support* consists mainly of the muscles of expiration, i.e., the muscles of the abdominal wall that keep the abdominal organs pressed within the concavity of the diaphragm. The *thoracic support* consists of the pericardium, heart and great vessels, and lungs, which attach directly or indirectly the upper surface of the diaphragm to the structures at the root of the neck and to the whole extent of the thoracic wall. The *costal support* consists of the abdominal ends of the lower six ribs. These are maintained in position by their passive articulation with the spine and the contraction of the external intercostal muscles.

Abdominal support

When the abdominal support gives way or weakens, the muscles of inspiration take over the balance between the inspiratory and expiratory muscles is upset. When this occurs, the thoracic and abdominal organs sustain the chief attack of inspiratory force. The walls of the abdomen are relaxed, the linea alba is open, and there is downward displacement of the diaphragm. The chest is deformed, the diaphragm does not move through as great an excursion as normally, and the thoracic muscles and movements of the thorax are called into greater play during respiration.

People with weakened abdominal support are usually overweight, the spinal axis is shifted forward, the upper thorax shows collapse in front, and there is flaring of the lower ribs. There is an upper dorsal kyphosis and often a cervical or lumbar lordosis. The thoracic supports of the diaphragm are weakened due to lack of abdominal support and due to the drag of the abdominal organs and the abdominal fat when in the erect position.

The diaphragm is depressed and partially flattened. In the erect position, the counterweight of gravity of the organs and abdominal fat and the loss of abdominal support interfere with the upward movement of the diaphragm during expiration.

These patients complain of thoracic musculoskeletal pains resulting from the stretching of the ligamentous attachments and the local changes that occur in the vertebral processes. There is often irritation of nerve roots, radicular pain, and muscular spasm. There is pain and soreness of the upper thoracic muscles from their stretch and the stress of breathing exerted on the muscles expanding the thorax. Further, these people frequently complain of considerable dyspnea in the upright position on slight exertion. Their vital capacity may be lowered. They may develop angina pectoris due to pooling of blood in the splanchnic area in the erect position and poor venous return of blood to the heart. They have postural cough.

It can be demonstrated that when the abdominal muscles are supported with a binder or belt, the diaphragm is raised, venous return to the heart increases, cardiac output increases as reflected in the ballistocardiogram, dyspnea

on exertion is decreased, and attacks of angina pectoris may disappear or become less frequent.

Thoracic support

The pull of the diaphragm on the thoracic structures or supports during inspiration is most important in understanding the movements of the thoracic organs during respiration.

The crura and the arcuate fibers of the diaphragm are firmly anchored to the spine, the pericardium and the inferior vena cava, and the right crus encircles the esophagus at its hiatus.

Through the attachment of the right and left crura of the diaphragm to the cardiac area, the pericardium and the strongly attached inferior vena cava, the insertion of the crural fibers is prolonged to the structures of the mediastinum but especially to the heart itself, the roots of the lung, and the great vessels and fibrous tissues in the upper aperture of the thorax and esophagus.

With each inspiration, the crura with a firm fixation to the spine exert their strength in drawing down and forward the structures of the mediastinum, and thus draw down the supports on which the central part of the diaphragm depends. When the thoracic or abdominal supports weaken, the active contraction of the crura is the most important factor in the production of visceral ptosis or the position of the thoracic and abdominal organs.

Costal support

The costal support, or the abdominal ends of the diaphragm that insert into the lower six ribs, is held in position by the articulation of the ribs to the spine and the contraction of the external intercostal muscles. The failure or weakening of this support throws greater weight on the abdominal and thoracic supports.

These three supports are necessary, then, for the normal functioning of the diaphragm. Let us now examine the chief function of the diaphragm, which is to maintain respiration.

EFFECT OF THE DIAPHRAGM ON RESPIRATION

With each inspiration the diaphragm descends and enlarges the thoracic cavity in the horizontal direction and displaces the viscera. The other muscles of inspiration enlarge the body walls in the transverse and anteroposterior direction. With each expiration the internal intercostals, transversalis, internal oblique, and rectus abdominis replace the viscera.

The organs within the thorax and abdomen are poised between the muscles of inspiration and expiration, and these sets of muscles strive for mastery. The diaphragm does not relieve the muscles of either the thorax or the abdomen of their respiratory function, but it adds its force to the muscles of inspiration

and is the chief and most powerful respiratory muscle. The movement of the diaphragm is responsible in large part for the expansion of the lower lobes of the lung and of the dorsal aspects of the upper lobes.

The type of respiration in which the diaphragm plays the greatest role is abdominal respiration. Here the respiratory movements are most noticeable in the upper part of the abdomen and the lower part of the chest. In thoracic breathing, the respiratory movement is most evident in the upper part of the chest, and the diaphragm plays little part. In most healthy adults, however, both types of respiration are observed, and one may predominate at times and fluctuate with the other.

The free movement of the diaphragm and the distensibility of the abdominal wall are important factors in normal respiration.

Examination of the chest

In the examination of the chest it is important to note, first of all, the type of respiration; that is, whether it is thoracic, abdominal or both. As the diaphragm enlarges the chest in the vertical direction it moves the abdominal contents downward and forward, the direction depending on the type of respiration. The total effect will depend on the action of the antagonists.

The movement of the lower and upper ribs and the excursion and direction of movement of the costal margins, as well as the movement of the abdominal wall, should be noted because the movements of the lower ribs—the 6th to the 9th—are correlated with the action of the diaphragm. The 11th and 12th ribs and often the 10th rib are functionally parts of the abdominal wall. The upper ribs, the 2nd to the 5th, and the manubrium sterni, represent the upper costal mechanism. They move and work independently of the diaphragm. The movement and excursion of the costal margins and the costal cartilages of the 6th to the 9th ribs should be noted because the excursion and direction of movement are governed by depth and type of respiration.

Excursion of costal margins

Some years ago, Hoover (5, 6) wrote extensively about the excursion of the costal margins and their relation to the position and contours of the diaphragm. It was his contention that the level of the diaphragm and its contraction determine to a considerable extent the excursion of the costal margins. That is to say, when the diaphragm is depressed, inspiration is followed by a medial motion of the costal margins because its contraction is able to overcome the action of the intercostals which are responsible for the upward and outward movement of the lower ribs. Conversely, the high position of the diaphragm is associated with greater outward movement of the costal margins because of the stronger contraction of the diaphragm.

Not infrequently in a patient with cardiac insufficiency, congestive heart failure and labored breathing, the costal margin motions move inward when

respiration is labored and thoracic in type, and move outward when respiration becomes quiet. This occurs without respect to the excursion, position, or contour of the diaphragm. It was this observation which aroused my interest in excursions of the diaphragm some years ago and later stimulated me to examine the movement of the diaphragm under the fluoroscope. I am convinced that the modification of the costal marginal motions is not a reliable guide to underlying pathologic conditions within the chest.

In 1929 Bray and Wilson (7) made a most important contribution to this subject and controlled their observations by fluoroscopic examination. With their conclusions I am in complete agreement. In essence, one can say that the extent of excursion of the costal margins depends on the depth of the respiratory effort, but the direction of their movement is governed by the type of respiration. The type of respiration and the lateral sway of the thorax are more important in determining the direction of the costal excursion than are the position and contour of the diaphragm.

The diaphragm, then, is the most important muscle of respiration. Its free movement enlarges the thoracic cavity in the horizontal position and is responsible in large part for the expansion of the lower lobes of the lung and the posterior aspects of the upper lobes. Inspiration is also aided by the other muscles of inspiration, and when the diaphragm weakens or loses function these muscles take over.

EFFECT OF CONTRACTION ON CONTOUR

Normal contour

In most persons the component fibers of the diaphragm form a continuous smooth sheet which gives the diaphragm the appearance of a uniform arc on either side of the heart, or in the lateral view an arc extending from the spine and posterior body wall forward to the anterior body wall. The right half of the diaphragm is usually higher than the left, and one can observe a clear costophrenic angle and the pericardial or inferior vena caval diaphragmatic angle in the anterior posterior position. The posterior pleural costal sinus and the anterior sulcus are seen in the lateral view.

During inspiration the contour changes very slightly and keeps its uniform smoothness. However, often during inspiration, especially when there is some degree of tracheal or bronchial stenosis, the contour of the diaphragm may be disturbed.

Physiologic variations

The physiologic variations in the diaphragmatic contour are of two general types: 1) double-cupola formation, due to prominence of the anterior portion of the median half of the right diaphragm (anteromedial bulge); and 2) multiple-cupola formation and individualization of costal components.

Anteromedial bulge

In the anteroposterior view, the diaphragm develops a prominent anteromedial bulge by dividing into two arcs midway between the lateral thoracic wall and the cardiac shadow on the right side. Under normal circumstances, this bulge is observed on deep inspiration, and it is more pronounced when the descent of the diaphragm is hindered by tracheal or bronchial stenosis. The median arc is higher and more convex than the lateral arc, and it is seen best in fluoroscopy in a slightly lordotic position. It becomes much less conspicuous on expiration, often disappearing, and it disappears on bending forward. In the lateral position, the median arc is seen in the anterior half of the chest, beginning about one fingerbreadth behind the sternum and ending about one fingerbreadth behind the heart shadow.

It has been established by anatomical study and section that the anteromedial bulge is due to the varying length, strength and position of the component muscle bundles of the diaphragm. The two cupolas are made up of a powerful posterolateral group of fibers and a weaker anteromedial group, both joining in the central tendon. The posterior lumbar fibers forming the crura diaphragmatica and the lateral costal fibers insert into the posterolateral part of the right wing of the central tendon. Contraction of these fibers pulls the diaphragm downward in a powerful manner.

The anteromedial part of the diaphragm is made up of short fibers arising from the sternum, ziphoid, and 7th and 8th ribs. It is depressed with relatively little force and is much weaker in muscular strength than the posterior fibers.

A further factor inhibiting the free and deep descent of the median part of the diaphragm is the passage of the inferior vena cava through the right leaf of the central tendon, where it is firmly anchored above.

The groove separating the anteromedial from posterolateral cupola is formed by the straddling action of the strong fibers from the crus medialis joining the fibers arising from the 9th rib. The median smaller bulge is formed anteriorly by the short anteromedial group of muscle fibers and posteriorly by the right wing of the diaphragm. The larger posterior cupola is formed by the powerful group of spinal muscle fibers.

There exist, then, these two groups of fibers, one arising anteriorly and medially, the other posteriorly and laterally. They insert into the central tendon. The posterolateral group are longer, stronger and more powerful than the anterior group, so that during inspiration, when there is an increase in the negative intrathoracic pressure, the downward movement of the anteromedial fibers is less than that of the posterolateral group, since they are more firmly fixed. The result is a bulge.

The left diaphragm is not subjected to similar change because of the absence of a large perforating vein such as the vena cava, and the presence of the heavy structure of the heart.

The anteromedial bulge must be distinguished from a subdiaphragmatic process that elevates the diaphragm irregularly. The points of importance are the location of the bulge, its size and form, its appearance on inspiration and disappearance on expiration or on bending forward, its exaggeration on inspiration in patients with bronchial or tracheal stenosis, and its disappearance on injection of a small amount of air into the pleural cavity.

Individualization of costal components

The second physiologic variable is individualization of costal components of the diaphragm. This is due to variable development of the muscle bundles leading from the lower six ribs. Normally, the component fibers from the ribs form a continuous smooth sheet so that the appearance of the diaphragm is a smooth arc. The variation under discussion produces either a series of cupolas or a scalloped appearance due to distinct, thick, band-like digitations or a series of slip-like extensions to the chest wall.

These irregularities in contour are seen most often in inspiration, and they are more common on the right side than on the left. They are due to individualization and hypertrophy of muscle bundles. They are observed most often in compensatory hypertrophy of the diaphragm and in asthma, emphysema or chronic bronchitis. A change in the configuration of the chest may lead to dislocation of the diaphragm or persistent muscular tone and passive tension.

The scalloped diaphragm must be differentiated from adhesions of the diaphragm. In the scalloped diaphragm, the irregularity disappears during expiration and the apices between the scallops point downward. In adhesions, the apices of the arc are directly upward.

Tenting and saucer-shaped deformities

Another physiologic alteration in the contour of the diaphragm that may be confused with adhesions is so-called "tenting" or saucer deformity. Tenting of the diaphragm (Matson) is encountered not infrequently when there is acute or chronic peribronchial infiltration of the lung. This is accompanied by ridigity, elongation and dilatation of the bronchi. During deep inspiration, a rigid bronchus produces a dimple on the basal surface of the lung due to inexpansibility both of the bronchus and of the infiltrated lung about it.

DISORDERS OF MOBILITY OR POSITION OF THE DIAPHRAGM

The resting level of the diaphragm and its mobility are dependent on the size and shape of the chest, the posture, the tone of the abdominal wall, the integrity of the phrenic nerves, the ability of the diaphragm to contract and the elasticity of the lung. Its position shifts under the influence of many factors, since it is concerned with maintaining the normal pressure relationships between the thorax and abdomen.

When the diaphragm is paralyzed, it becomes immobilized. It ascends in the

chest due to the absence of movement during respiration and the intra-abdominal pressure. Since every organ within the body cavity swings with the respiratory tide, the respiratory balance is upset by paralysis of the diaphragm. The balance between the muscles of inspiration and expiration is upset and the organs of the thorax and abdomen are displaced from their normal position. In some instances, this displacement causes no symptoms or disorders of function that call attention to the difficulty; in others, the displacement causes disorders of function and hence symptoms.

There are two disorders of the diaphragm that are concerned with its high position and its diminished or absent movement that require comment: paralysis and eventration.

Paralysis of the diaphragm

Paralysis of the diaphragm is exceedingly common. It occurs in a variety of circumstances that interrupt the nerve supply to the diaphragm. It is seen most often following poliomyelitis and surgical section of the phrenic nerve for treatment of tuberculosis.

The diagnosis may be suspected from unequal expansion of the costal margins, which are greater on the involved side due to excessive action of the intercostal muscles, the absence of inspiratory protrusion of the abdominal wall, descent of the cricoid cartilage on inspiration, and a high level of thoracic resonance and decreased breath sounds on the paralyzed side.

The definitive diagnosis is made by roentgen ray examination which shows the diaphragm to be elevated and immobile during respiration and with paroxysmal movement during sniffing.

These patients may have dyspnea on exertion but experience very little discomfort during rest.

Following paralysis of the diaphragm and its high elevation, the abdominal musculature attempts to make the proper adjustments by supporting the diaphragm in its high position. Since there is a pronounced shift in the movement of the organs during the respiratory tide, the abdominal viscera become greatly distorted. These distortions have been studied by Stansbury (8) and, to a lesser degree, by Graham (9). In most cases no symptoms arise following the distortion, but in some cardiospasm follows the change in position of the esophagus, and in others fatal gastroduodenal obstruction has ensued.

Although paralysis of the diaphragm is seen most often in diseases of the central nervous system such as poliomyelitis, and following crushing or division for the treatment of tuberculosis, there are other causes due to compression of the phrenic nerve at any point during its course. When phrenic nerve palsy is observed in any patient with a mediastinal mass, it is usually due to a tumor rather than an aneurysm. In my own experience, carcinoma of the lung and carcinoma of the breast with metastases to the mediastinum have

been the two commonest tumors causing phrenic paralysis. When paralysis is associated with a diaphragmatic hernia, the hernia usually extends through the central tendon. In any patient with diaphragmatic paralysis who shows no mediastinal mass and no other signs of central nervous system disease, one should entertain the possibility of a peripheral neuritis following diphtheria, alcoholism, or nutritional deficiency.

Eventration of the diaphragm

Of perhaps greater importance, insofar as symptoms are concerned is congenital and permanent eventration of the diaphragm which causes its elevation and results in restriction of peristaltic movement. This disorder may produce very few symptoms except dyspnea on exertion, paroxysmal dysphagia and the easier swallowing of solid food than of liquids. Some patients develop ulcer of the esophagus or stomach associated with the mechanical deformity and malposition of the stomach and esophagus.

The type of eventration that I shall discuss is the acquired or transitory type, which is due to accumulation of gas in the stomach or in the splenic flexure immediately below the diaphragm. These patients, like those with esophageal hiatal hernia, belch much gas, and many of them are uncomfortable and an annoyance to their families. When the gas is under excessive tension, the left dome of the diaphragm is displaced upward into the thorax. The patients complain of shortness of breath, fullness in the abdomen, "wind around the heart," and palpitation. Some patients have excessive salivation and attacks of sweating.

In patients with spasm of the lower end of the esophagus due to simple ulcer, enormous quantities of gas may accumulate in the stomach and cause intense pain, increased each time food or saliva is swallowed admixed with air. The enormous gas bubble is due to failure of swallowed air to escape upward, just as it interferes with the passage of food downward. When an excessive amount of gas accumulates in the splenic flexure due to increased aerophagia or intestinal carbohydrate indigestion, the cardiac end of the stomach may be displaced so that the angle between the esophagus and stomach is more acute. Gas collects in the stomach as well as the splenic flexure and causes discomfort and elevation of the diaphragm.

Intestinal carbohydrate indigestion is not an uncommon disorder. When it is severe enough to cause abdominal pain, discomfort, diarrhea, and increased intestinal gas which distends the colon and raises the diaphragm, it may produce symptoms that direct attention to either the thorax or the abdomen. Intestinal carbohydrate dyspepsia has been studied intensively in the past by Hurst and Knott (10) in England, and by Owles (11) of the Thorndike Memorial Laboratory in Boston.

The excess gas in the splenic flexure is due to the bacterial fermentation of

starch in the large intestine. During the day, gas collects in the splenic flexure and causes discomfort, often mistaken for gastric flatulence, and so gives rise to aerophagia. During the night, when the splenic flexure is no higher than the pelvic colon or rectum, the gas moves onward and discomfort occurs only when gas is passed. The stools are acid, contain starch granules, and produce gas on incubation.

When the patient is in the horizontal or recumbent position, gas can escape from the stomach when it reaches the pylorus. In the morning no excess gas is present, but following each meal the quantity increases until the afternoon when the rise in pressure is sufficient to cause pain and discomfort and the diaphragm is displaced into the thorax. Immediate relief follows passage of the stomach tube. Lying down will give partial relief, since some gas passes into the small intestine and is expelled by anus but enough remains in the splenic flexure to dislocate the cardia and cause pain.

Thus, a high position of the diaphragm may be observed when there is an excessive amount of gas in the stomach or splenic flexure and increased intra-abdominal pressure. The symptoms caused by such a situation are usually due to encroachment on the pulmonary space and the increase in abdominal pressure.

Spasm of the diaphragm

The diaphragm may show tonic or clonic spasm. Clonic spasm is most often associated with hiccup. When there is a sudden and intense contraction of the diaphragm and the negative pressure in the chest cavity is lowered abruptly, the vocal cords close suddenly and the peculiar sound of hiccup appears. This clonic contraction occurs irregularly, so that hiccup is produced during some contractions and not during others, depending on the position and tone of the diaphragm and the force of the contraction. During the spasms the epigastrium is thrust forward, the intercostal muscles retract, and the chest is slightly elevated.

It is generally recognized that clonic spasm of the diaphragm occurs in association with a variety of systemic disorders and local conditions within the chest or abdomen, and this is an abnormal muscular disorder that is often difficult to control. The type of clonic spasm to which I wish to direct attention is that which is synchronous with the heart beat. In some patients the contraction of the diaphragm is due to stimulation of the phrenic nerves by cardiac activity, with hiccup as a result, or the diaphragm may contract synchronously with the heart beat, without hiccup.

Contraction of the diaphragm synchronous with heart beat has been described by Karelitz (12) in an infant with tetany and by Söderstrom (13) in a man with gastric tetany. A recent study by Lepeskin (14) indicates that hiccup is due in some instances to stimulation of the phrenic nerve by cardiac activity. His patients had hiccup following surgical operations, and in one

case the patient suffered from arteriosclerotic heart disease. Lepeskin noted that with each contraction of the diaphragm a distinct artefact was observed in the electrocardiogram. The close anatomical relationship between the heart and the phrenic nerves suggested to him that stimulation of the phrenic nerves by electric currents produced during the heart beat might be responsible for some forms of hiccup and diaphragmatic tic. He recalled the old experiment of Mattececi in which contractions of one frog muscle was achieved by laying the nerve of this muscle across another contracting muscle and thought that there might be an analogy in the case of the heart and the phrenic nerve.

In Lepeskin's studies of the relation of hiccup and the electrocardiogram, the hiccup sounds were recorded synchronously with three leads of the electrocardiogram. In three cases the hiccup movements caused electrocardiographic artefacts which could be confused with V waves or with auricular and ventricular premature beats. It was of considerable significance that the hiccup sounds and the artefacts always occurred between 0.17 and 0.4 seconds after the beginning of the QRS complex of the electrocardiogram, and in some cases two successive heart beats were followed by hiccup movements. Lepeskin postulated that the hiccup was caused by stimulation of one of the phrenic nerves by the electric currents registering as the QRS complex.

In these cases it has been suggested that the phrenic nerves were hyperirritable due to a decrease in the ionized serum calcium or to alkalosis.

Hiccup and heart beat

It has been demonstrated that the phrenic nerve becomes excitable by cardiac action potentials when there is a decrease in the concentration of ionized calcium, which decreases the accommodation of the nerve and thus increases its irritability. Thus, hypocalcemia or alkalosis have been found associated with diaphragmatic contraction synchronous with the heart beat. Inasmuch as a decrease in the ionized calcium of the blood will not cause tetany unless the potassium content of the blood is normal, it follows that in the presence of a hypocalcemia one may not have tetany if there is hypokalemia at the same time.

These observations direct attention to the relation of biochemical changes to increased irritability of the phrenic nerves, and their increased susceptibility to mechanical stimulation by the heart contraction. Scherf noted diaphragmatic contraction synchronous with the heart beat in dogs which was interrupted by phrenic nerve section. This was observed under anesthesia and following exposure of the heart or the diaphragm.

It is important, then, to recognize diaphragmatic contraction synchronous with the heart beat, because it may be unassociated with the sound of hiccup, and there may be a form of singultus that can be controlled by calcium therapy or the prevention of overventilation.

In summary, the diaphragm may contract synchronously with the heart

beat with or without the sound of hiccup. It has been observed in patients with gastric tetany and alkalosis, in low-calcium tetany, in hyperventilation and alkalosis, and following abdominal operations.

Another form of spasm of the diaphragm is tonic spasm. While this has been described rarely in rabies, tetanus, and strychnine poisoning, it is seen most often in patients with anxiety states or situational conflicts.

SUSTAINED CONTRACTION OF THE DIAPHRAGM

Patients with sustained contraction complain of respiratory distress characterized by inability to get a full breath. These cases have been studied especially by Wolf (15). Usually inspiration is jerky, so that the excursion of the diaphragm in inspiration exceeds that in expiration and the diaphragm, therefore, assumes a progressively lower position. In this state, there is a feeling of inability to take a breath, or shortness of breath takes place. Often there are other symptoms such as pallor and sweating, and sometimes there is thoracic pain and difficulty in swallowing. The diaphragm is in a state of spasm in the inspiratory position.

DIAPHRAGMATIC FLUTTER

A rare disturbance in motility of the diaphragm that has attracted attention over the past 25 years is diaphragmatic tic or flutter. In this arrhythmia, there are rapid rhythmic contractions of the diaphragm, occurring in attacks. They may be unilateral, or bilateral, and the diaphragm may contract from 70 to 200 times a minute.

These attacks of flutter have been observed following encephalitis lethargica (16), as a feature of overventilation tetany, following fracture of the xiphoid, in drug addicts, or as a muscular tic of unknown cause in which the diaphragmatic muscle itself appears to be at fault. It has been postulated by Harris and Scherf (17) that the diaphragm may set up its own rhythm independent of phrenic nerve supply.

According to the literature, the three commonest symptoms are breathlessness, pain in the chest, and palpitation. Breathlessness is commonest, and it is sudden in onset and may continue for days. Pain in the chest is felt at the site of attachment of the diaphragm to the ribs, in the epigastrium, or over the precordium. It has been reported as radiating to the left arm or shoulder. These are the cases that are confused with attacks of angina pectoris, the most famous of them being the one first reported by Porter.

Examination of the patient during attacks discloses rapid tick-tock sounds of unequal intensity, occurring throughout the chest but most marked at the lung bases. The heart rate is slow, and fluoroscopic examination of the chest shows rapid up-and-down excursions of the diaphragm. In some cases it is unilateral.

The diagnosis is established by hearing the tick-tock sounds in the chest and visualizing the rapid up-and-down movements of the diaphragm under the fluoroscope.

Palpitation is not present in most cases, but when it is conspicuous it may be confused with paroxysmal tachycardia.

The signs that aid in diagnosis are rapid pulsation in the epigastrium, independent of the heart beat but regular or slightly variable in rate and intensity, diminished expansion of the thorax, and extracardiac sounds suggesting a to-and-fro murmur, tick-tock rhythm, or a friction rub.

The diagnosis is confirmed by fluoroscopy and the rapid flutter of the diaphragm.

PARADOXICAL MOVEMENT OF THE DIAPHRAGM

One form of diaphragmatic movement that has attracted attention is paradoxical movement. It is favored by any condition tending to make intrapleural pressure unusually low or to weaken the force of diaphragmatic contraction. It may occur when the diaphragmatic musculature is weakened by partial paralysis or other causes. Frank paradoxical movement is strongly suggestive of diaphragmatic paralysis.

Complete paralysis is not always accompanied by paradoxical movement, because some patients use their ribs so little in respiration that intrathoracic pressure is lowered only a little during inspiration. Also, extensive adhesions may prevent visible respiratory movement of any sort.

Slight paradoxical movement on quiet inspiration is known as Kienbock's phenomenon. Greater paradoxical movement is called Bittdorf's phenomenon. When a patient attempts to inspire with the mouth and nares closed there is a great increase in the negative intrathoracic pressure. The paralyzed half of the diaphragm rises in the chest, while the unparalyzed half descends; when neither side is paralyzed both sides rise a little. When one side is paralyzed, it rises high enough to satisfy the high intrathoracic pressure bilaterally, thereby allowing the unparalyzed side to descend.

When a patient sniffs suddenly and deeply, a paralyzed or even incompletely paralyzed hemidiaphragm undergoes pronounced paradoxical movement.

With a normal diaphragm, paradoxical movement occurs in pneumothorax only when the intrapleural pressure on inspiration is sufficiently high to overcome the contractile force of the diaphragm. If the mediastinum is not fixed, it may be displaced and the change in intrapleural pressure may be entirely spent in causing a pendulous movement of the mediastinum. When pneumothorax and homolateral diaphragmatic paralysis coexist, paradoxical movement is regularly present unless there are diaphragmatic adhesions.

Thus, we see that disturbances in movement of the diaphragm have an effect on respiration. Their analysis is helpful in the diagnosis of a variety of

primary and secondary disorders of the diaphragm and in intrathoracic and intra-abdominal disease.

CIRCULATION

In addition to the effect that movement of the diaphragm has on normal respiratory function, it also plays an important part in maintaining the normal circulation. It has sometimes been called the "respiratory pump" (18) or the "second heart," but during conditions of rising central venous pressure the pumping function may fail or weaken, and in paralysis the pumping action is lost.

Diaphragmatic contraction and its effect on circulation of blood

The effects of diaphragmatic contraction and changes in intrathoracic and intra-abdominal pressure on the movement of blood from the abdomen and from the upper and lower extremities and head to the heart have been studied extensively in our clinic by Wilkins and his associates (19). They have examined normal persons, individuals with hypertension, and patients with heart disease, with and without congestive heart failure. Studies on the effect of movement of the diaphragm on circulation have been made by others in the past, with the following conclusions.

1. During inspiration the intrathoracic pressure is lowered by the descent of the diaphragm, and the intraperitoneal pressure is maintained at a fairly constant level (20).

2. The fluctuations in intrathoracic and intra-abdominal pressures during respiration have influence on the circulation of blood from the upper and lower half of the body and trunk, as well as blood flow from the splanchnic bed and liver.

As a breath is being taken, the right crus of the diaphragm contracts and forces blood from the inferior vena cava to the right auricle, so that an increased supply of blood is sent to the right side of the heart. The right crus also exerts its force on the left auricle through its attachment to the dorsal wall of the pericardium through the central tendon. Traction on the pericardium from below has two effects: it tends to empty the left auricle, and at the same time it acts on the terminations of the pulmonary veins to close them. During inspiration the action of the crus assists in increasing the venous blood to the lungs and in decreasing the outflow to the left auricle. During expiration the reverse is true.

During inspiration the central tendon at the point of attachment to the vena cava does not display much movement, and the foramen of the cavity does not change in area during the movements of the diaphragm. Hitzenberger (21) was able to visualize the cava below the diaphragm in a single patient by x-ray and stated that during inspiration there was slight narrowing of the vein.

The evidence suggests, then, that at the beginning of inspiration the blood

flow to the heart through the inferior vena cava is accelerated. There is also good evidence that the blood flow from the liver into the cava is increased during inspiration (22) due to the inspiratory compression of the liver and its decrease in size. After the beginning of inspiration there is a decrease in the venous return in the infraportal and caval systems; with expiration the conditions are reversed. It is concluded, then, that in quiet respiration and in normal people the blood flow from the head and arms is increased during inspiration and the blood flow from the legs is decreased. During expiration, the reverse is true.

The effect of increasing the intrathoracic and intra-abominal pressure on return blood flow to the heart during periods of forced inspiration and by the use of the Valsalva maneuver has been studied intensively by Wilkins and others in our clinic. In a normal subject, when the Valsalva experiment is performed with a catheter in the vena cava below the diaphragm, there is a temporary cessation of blood flow from the cava, and the blood remains below the diaphragm for some seconds. The absence of flow at this point suggests that the intrathoracic and intra-abdominal pressure temporarily exceeds the central venous diastolic pressure, and until venous pressure builds up to overcome this, there is a decrease in flow of blood into the heart.

When, however, there is an increase in the central venous pressure such as one sees in congestive heart failure, the Valsalva test causes no change in blood flow from the hepatic veins and vena cava, and blood flows freely into the heart. The mechanism for controlling blood flow as influenced by intrathoracic and intra-abdominal pressure relations and the breakdown of the mechanical mechanism within the right atrium due to a rising venous pressure (18) have been studied by Stucki, Judson and Wilkins (22). Hitzig (23) has also studied the effect of increased venous pressure on blood flow during respiration and the "hepatojugular" reflex phenomenon, which is an example of the breakdown in the normal pressure relations.

Some of these effects are illustrated by the following case.

Mr. A., 56 years of age, complained of shortness of breath and cough and had signs of congestive heart failure with distention of neck veins, rales at both lung bases, enlargement of the liver, and edema of the extremities. During inspiration the neck veins enlarged, and pressure over the liver with the hand likewise increased their size, so that "inspiratory and manual" hepatojugular reflex phenomena were present. The breathing was forced so that the accessory muscles of respiration were used. The diaphragm was elevated by x-ray, there were strong contractions of the diaphragm on inspiration, and the rib margins were pulled inward at the costal margins with each inspiration. More careful study of the venous pressures showed that during inspiration and descent of the diaphragm, the venous pressure in the jugular vein increased and the manual hepatojugular pressure caused an increase in jugular vein pressure. The

right atrial and end diastolic pressure were elevated on cardiac catheterization, and during the Valsalva maneuver, there was no interruption of the venous return to the right atrium from below the diaphragm. When Diodrast was introduced below the diaphragm through a small catheter during the period of congestive failure, the dye could be seen below and above the diaphragm for five seconds without the Valsalva maneuver, and when Diodrast was injected during the Valsalva maneuver, it was also found above the diaphragm. These observations indicated that during the heart failure the central venous pressure rose and was transmitted to the inferior vena cava. During inspiration the pressure in the cava rose still further due to contraction of the diaphragm and the increased pressure in the abdomen, so that blood flowed freely through the cava during the Valsalva maneuver.

Following recovery from heart failure the conditions were reversed and the end diastolic pressure in the right atrium was lower, the peripheral venous pressure decreased and the hepatojugular reflex phenomenon disappeared. Now, when Diodrast was injected below the diaphragm during the Valsalva maneuver, it was held there for a short period of time. In short, the situation was the same as in a normal person without heart failure. The intrathoracic pressure during the Valsalva maneuver is greater than the intra-abdominal and caval pressure, so that blood fails to flow into the heart.

These various observations of the effect of diaphragmatic movement on the circulation can be summarized as follows: The contraction of the diaphragm and the pressure changes that follow with phases of respiration assist in the movement of blood from the periphery to the heart. When the central venous pressure rises as in heart failure, these normal relations break down. The intrathoracic and intra-abdominal pressure changes induced by diaphragmatic contraction, together with the central venous pressure, are all-important in maintaining this normal balance of blood flow.

DISEASES INVOLVING THE DIAPHRAGM

The diaphragm is the site of inflammatory diseases, primary and secondary tumors, hemorrhage, edema, and degeneration.

The common inflammatory diseases are those arising from the lung, pleura, peritoneum, or pericardium, and include tuberculosis, bacterial infections of the lungs and peritoneum, Coxsackie virus infections, and parasitic infections such as trichinosis.

Primary tumors of the diaphragm are rare. The only primary malignant tumor I have observed was a rhabdomyosarcoma, and the presenting feature was hemorrhagic pleural effusion. Benign tumors include fibromas and lipomas and can be removed successfully. Only about one-half produce symptoms; the other half are recognized by x-ray.

Secondary tumors are exceedingly common, and they may destroy much of

the diaphragmatic muscle and interfere with its movement. These tumors often spread in the great subserous lymphatics and form great layers on the diaphragm. Peritoneal involvement is likely to be more common than pleural. Metastases are seen most often in cancer of the abdominal organs, especially the stomach, and from the breast and lung.

Symptoms referable to the diaphragm, usually in the form of diaphragmatic pleurisy and dyspnea, are usually present in 20 per cent of cases, and there may be no movement of the diaphragm due to infiltration with tumor or upper abdominal adhesions and fixation of tissues by tumor.

Hemorrhages into the diaphragm follow trauma and have been seen in rupture of blood vessels, as in aneurysm of the aorta at the level of the diaphragm, or in association with hemorrhagic disorders of scurvy and leukemia. One finds blood in the lymphatics of the diaphragm following bleeding into the peritoneal cavity.

Edema is encountered in cardiac insufficiency and in nephrosis. Degenerations of the muscle, aside from those following paralysis or congenital eventration, occur under a variety of circumstances such as following inflammations or during the course of primary muscular diseases.

CONCLUSIONS

In this lecture, I have discussed some of the congenital and acquired defects of the diaphragm, and I have pointed out the importance of the movement of the diaphragm on respiration and on circulation. Finally, I have directed attention to some uncommon diseases of the diaphragm that cause symptoms.

My purpose in directing attention to the diaphragm is to stimulate further studies concerning its function in respiration and circulation and to relate these studies to pulmonary function. Further, with the great improvements in surgical technique, we are able to relieve many patients of annoying and frequent symptoms by repair of hernias, which are increasing in frequency, and we are able to learn more about the normal and abnormal diaphragm.

The diaphragm acting as a respiratory pump is an important muscle of the human body, and its normal action is essential for maximum well being.

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A HITHERTO UNDESCRIBED VULNERABILITY OF THE JUXTAMEDULLARY GLOMERULI IN LIPOID NEPHROSIS

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As is well known, lipoid nephrosis is characterized clinically in its earlier stages by marked proteinuria, hypoalbuminemia, edema and hypercholesterolemia, without hypertension, nitrogen retention, diminished phenolsulphonphthalein excretion or impaired urea clearance, and with only minimal or no hematuria. Recovery from this "pure nephrotic stage" may be complete; or, as time passes, definite clinical evidences of glomerulo-tubular damage (impaired urea clearance, nitrogen retention, diminished phenolsulphonphthalein excretion, hypertension, and increase in hematuria) may make their appearance, with gradual progression to renal failure and death in uremia.

Pathologically, in the early periods of the "pure nephrotic stage" there are ordinarily deposits of lipoids, partly anisotrophic, in the tubular epithelium; but aside from slight lipoid deposits in glomerular cells, the glomeruli, in spite of the marked albuminuria, ordinarily appear essentially normal on cursory inspection, and it is only by careful examination that slight, focal thickening of some of the capillary basement membranes can be discerned. With the passage of time, however, glomerular alterations of a more definite type may occur, and may become progressively more severe and extensive. In this process, the basement membranes of the tuft capillaries tend to become increasingly thickened, and focal hyaline deposits appear in the tufts and increase progressively, leading gradually to the complete obliteration of the normal glomerular architecture. This "intercapillary" or "membranous" glomerulosclerosis, which leads to death from renal failure, is quite different from the ordinary progressive, proliferative glomerulonephritis, and can readily be distinguished from the latter histologically. In contrast to proliferative glomerulonephritis, in cases of the glomerulosclerosis of lipoid nephrosis that are uncomplicated by a focal nephritis from intercurrent infection (such as the pneumococcal peritonitis and septicemia to which nephrotics are prone) or by a superimposed arteriosclerotic nephritis resulting from arteriolosclerosis developing in the hypertensive stage, proliferation of the endothelial and epithelial cells of the tuft is slight or absent; inflammation is negligible or absent; and while small focal adhesions between the tuft and Bowman's capsule are not uncommon, epithelial crescents are either absent or extremely rare. The gradual and progressive hyalinization and solidification of the tuft, in the absence of conspicuous

inflammation or cellular proliferation at any stage of the process, presents a picture altogether different from the inflammatory-proliferative lesions of the tuft which can lead to destruction of the tuft architecture and eventual scarring and hyalinization of the tuft in proliferative glomerulonephritis. While features of the clinical picture of lipoid nephrosis may occur in other renal affections (e.g., amyloid, diabetic glomerulosclerosis), true lipoid nephrosis exists as a separate disease entity, independent of other renal diseases which may simulate it clinically.

The etiology of lipoid nephrosis is unknown. The pathogenesis of the glomerular lesions (i.e., the nature of the increased permeability of the glomeruli to albumin, and the mechanism of the process responsible for the gradual development of the obliterative glomerular sclerosis which leads to the death of many of the patients with lipoid nephrosis) is completely obscure. The purpose of the present paper is to draw attention to a hitherto undescribed but characteristic peculiarity in the development of this sclerosing glomerular lesion.

In brief, the peculiarity, strikingly evident when once observed, consists in the fact that, with regularity, the glomeruli that are the first to become involved in the obliterative process, and the first to undergo destruction as the process advances, are the so-called juxtamedullary glomeruli, i.e., those situated in the zone at the level of the cortical-medullary junction (Fig. 1). This peculiar vulnerability of the juxtamedullary glomeruli invites consideration in the investigation of the completely obscure pathogenesis of the life-threatening obliterative glomerulosclerosis of lipoid nephrosis.

The series upon which the present observations are based consists of 20 cases of clinically and pathologically typical lipoid nephrosis (Table I). It is well known that true lipoid nephrosis is primarily a disease of childhood, occurring only occasionally in adults. In the present series, nineteen patients were between 1½ and 16 years of age at death; one was 24 years of age. The majority were between 2 and 6 years of age. Before the era of antibacterial chemotherapy, the life of patients with lipoid nephrosis was often terminated by intercurrent infection (prominently, and peculiarly, by pneumococcal peritonitis) before the disease had run its course to recovery or to the development of hypertension and renal insufficiency. In the present series, which includes cases that occurred both before and after the introduction of antibacterial chemotherapy, the duration of life after the disease first manifested itself by edema ranged between 6 weeks and 5 years. 5 of the 20 patients died during the first six months following the onset of noticed edema; 5 died between six months and one year after the onset; 6 during the second year; 1 during the third year; 2 during the fourth year; and one five years after the onset. The cases provide, therefore, an excellent series for the study of all stages of the renal lesions.

TABLE I

TABLE I

Twenty Fatal Cases Beginning As "Pure Lipoid Nephrosis"

Autopsy Number	Sex Color Age	Lived after Edema First Noticed	Character and Localization of Glomerular Lesions				Hypertension after Initial Period	Elevated N.P.N. after Initial Period	Cause of Death
			Focal thickening of capillary basement membranes	Obliterative lesions in J-M[1] zone only	Diffuse obliterative lesions, predominantly and older in J-M[1] zone	Extreme obliterative lesions throughout cortex			
8162	M. W., 4½ yrs.	5½ mos.	Sl.	–	–	–	–	–	Pneumococcal peritonitis
10902	F., W., 5 yrs.	7 mos.	Sl.	–	–	–	–	–	Fever, sudden death, no cause found
12176	F., C., 1½ yrs.	6 wks.	Sl.	–	–	–	–	–	Pneumococcal peritonitis
15743	M., C., 8 yrs.	2 yrs.	+	–	–	–	–	–	Pneumococcal peritonitis
15090	M., C., 3½ yrs.	4 mos.	+	+	–	–	–	–	Pneumococcal peritonitis
17845	M., W., 2 yrs.	1 yr.	+	+	–	–	Intermittent	Intermittent	Pneumococcal peritonitis
18175	F., W., 3 yrs.	5 mos.	+	+	–	–	–	–	Pneumococcal peritonitis
23055	M., W., 2 yrs.	6½ mos.	+	+	–	–	–	+	Shock following paracentesis
25575	M., C., 2½ yrs.	5 mos.	+	+	–	–	–	–	Pneumonia
9874	F., W., 16 yrs.	9½ mos.	+	–	+	–	+	+	Extreme anemia
22548	M., W., 3 yrs.	1½ yrs.	+	–	+	–	+	+	Uremia
23124	F., C., 24 yrs.	2 yrs.	+	–	+	–	+	+	Uremia
23302	M., W., 5 yrs.	1⅔ yrs.	+	–	+	–	+	+	Uremia
23529	M., W., 2½ yrs.	6½ mos.	+	–	+	–	+	+	Uremia
24836	F., C., 16 yrs.	2 yrs.	+	–	+	–	+	+	Uremia
25354	M., W., 3½ yrs.	1½ yrs.	+	–	+	–	+	+	Torula infection
19942	M., W., 6 yrs.	2½ yrs.	+	–	–	+	+	+	Uremia
22374	F., W., 3 yrs.	3¾ mos.	+	–	–	+	+	+	Uremia
22509	M., W., 5½ yrs.	3½ yrs.	+	–	–	+	+	+	Uremia
25005	M., W., 7 yrs.	5 yrs.	+	–	–	+	+	+	Uremia

[1] J-M = juxtamedullary.

Seven of the patients died while in the "pure nephrotic stage," as defined in the first paragraph of this paper. In 3 of these 7 cases (8162, 10902, 12176) the only structural abnormality that could be detected in any of the glomeruli in the paraffin sections was a very slight focal thickening of the capillary basement membranes, requiring meticulous examination to detect (Fig. 2). In one case of two years duration (15743) the membrane thickening was more advanced (Fig. 3), but even in this case, in many of the glomeruli it was not conspicuously evident on cursory inspection. In the remaining 3 cases dying in the "pure nephrotic stage" (15090, 18175, 25575), in addition to focal thickening of capillary basement membranes there were focal deposits of hyaline in glomerular tufts, leading to obliteration of the capillaries and solidification of part or all of the tuft. These latter lesions were *limited to the juxtamedullary glomeruli* (Figs. 4, 5, 6, 7, 8, 9).

In two other cases (17845, 23055) in which there were obliterative glomerular lesions *limited to the juxtamedullary glomeruli* (Figs. 10, 11), there had been a moderate nitrogen retention which, in one case (17845) was intermittent and was accompanied by intermittent moderate hypertension.

In 11 of the 20 cases of the series, the process of obliterative glomerulosclerosis was no longer confined to the juxtamedullary zone, but had spread to glomeruli in the cortex between the juxtamedullary region and the capsule. In 7 of these cases (9874, 22548, 23124, 23302, 23529, 24836, 25354) it was clear that the obliterative process had begun in the juxtamedullary glomeruli and that the glomeruli elsewhere in the cortex had been damaged later, for the oldest and most marked lesions were concentrated in the juxtamedullary zone. In the remaining 4 of the 11 cases with widely distributed obliterative glomerular lesions (19942, 22374, 22509, 25005) the process was so far advanced that differences in the degree of involvement in the different levels of the cortex were no longer distinguishable.

Hypertension and elevated non-protein nitrogen had been present clinically in all of the 11 cases in which obliterative glomerular lesions of varying degree were present throughout the cortex, and death resulted from uremia in 9 of them.

DISCUSSION

It is clear from the study of these cases that the juxtamedullary glomeruli (i.e., those situated at the cortical-medullary junction) are the first to be affected by the hyalinizing, solidifying process that leads to glomerular destruction and to uremia in patients with lipoid nephrosis. The focal thickening of the capillary basement membranes, which is the first visible glomerular alteration in lipoid nephrosis, is so slight in the early stage of its development that the alteration often borders on the equivocal, and may be absent in most of the glomeruli. Differences between the degree of involvement of the juxta-

medullary glomeruli and those elsewhere in the cortex are not readily discernible at this stage; but as the process advances, and the focal intercapillary deposits of hyaline that lead progressively to obliteration of the structure of the glomeruli appear, it is quite clear that this damage begins first in the juxtamedullary glomeruli, and is at first limited to those glomeruli. As the deposition of hyaline gradually progresses in severity and extent, glomeruli between the juxtamedullary zone and the capsule begin to become involved also, and with the passage of time the obliterative glomerular damage spreads throughout the entire cortex, the sub-capsular zone being usually the last in which these glomerular lesions appear. Up to the point at which glomeruli throughout the cortex have become so severely altered that no appreciable differences in the degree of damage in the different regions of the cortex can any longer be detected, it is always plainly evident that the oldest and most severe lesions are concentrated in the juxtamedullary glomeruli.

The question naturally arises as to whether the juxtamedullary glomeruli are similarly predisposed to other types of glomerular injury. No such uniform tendency to early or more severe involvement was detected in an examination of a number of cases of each of the following types of renal injury, including relatively early stages of each condition: renal amyloidosis, diabetic glomerulosclerosis, arteriolosclerotic nephritis, acute and subacute proliferative nephritis, disseminated lupus erythematosus, and the focal glomerulonephritis associated with periarteritis nodosa. In individual cases of diabetic glomerulosclerosis, proliferative glomerulonephritis and disseminated lupus erythematosus there were a relatively larger number of the more advanced lesions in the juxtamedullary glomeruli, but in an equal or greater number of cases of the same condition there was no difference in the lesions in the different layers of the cortex, or even, in some cases, a greater prominence of more advanced lesions in the non-juxtamedullary glomeruli. It may be remarked that while the focal, acute necrotizing type of glomerulonephritis that may occur in association with periarteritis nodosa produced in the rabbit by hypersensitivity to foreign antigens (2) has a tendency (though not a constant one) to attack the glomeruli of the juxtamedullary region of the rabbit's kidney more prominently than glomeruli in other parts of the cortex, this was not found to be the case in the present study of the anatomically similar, focal acute glomerulonephritis that occurs in association with periarteritis nodosa produced by hypersensitivity in the human being (2).

It would be of considerable interest to know whether the abnormal escape of protein that characterizes lipoid nephrosis begins in the juxtamedullary glomeruli or diffusely throughout the cortex. The present material throws no light upon that question. A more pointed study of the location of the nephrons which first exhibit a deposition of lipoid in the early "pure nephrotic stage" would be of interest in this connection.

Since it is stated that in the glomerulosclerosis ("chronic membranous nephritis") of lipoid nephrosis "histologically no glomerulus is spared and the changes are remarkably uniform" (1), it should particularly be pointed out that the present study does not at all conform to that statement. Indeed, the substance of the present paper stresses the inequalities in the degree and extent of the glomerular involvement in different regions of the cortex. These cases show plainly that the glomeruli in even any one region, including those in the vulnerable juxtamedullary zone, are not all simultaneously and uniformly affected. On the contrary, definitely altered glomeruli may be found adjacent to glomeruli that are essentially normal in appearance, and completely destroyed glomeruli adjacent to only slightly damaged ones (Fig. 12). The injury responsible for the glomerulosclerosis in this disease is not one to which all or even most of the glomeruli react at the same time with uniform intensity. The reaction is, on the contrary, decidedly focal in its evolution. Fig. 12 illustrates that the focal nature of the process is apparent in the adult as well as in the child, and is not a peculiarity of the kidney of the infant and young child. The focal nature of the process, gradually spreading to involve destructively more and more glomeruli, is consonant with the gradual clinical transition from the "pure nephrotic stage" to one of increasing glomerular damage as evidenced by increasing hematuria and by the gradually progressive development of hypertension, impairment of urea clearance, and renal failure.

The reason for the greater susceptibility of the juxtamedullary glomeruli to the injurious process which leads to the destructive glomerulosclerosis of lipoid nephrosis is obscure. Trueta and his coworkers (3) have shown that the circulation of the juxtamedullary glomeruli differs both anatomically and functionally from that of the glomeruli elsewhere in the cortex. In the case of the latter glomeruli, as is well known, the efferent arteriole is decidedly smaller that the afferent arteriole, an arrangement favorable to the filtration function of the glomerulus. In contrast, Trueta and his colleagues found that the efferent arterioles of the juxtamedullary glomeruli are as large or larger than the afferent arterioles. These glomeruli, therefore, do not possess the pressure-raising vascular arrangement that is characteristic of the other renal glomeruli, and the process of filtration through their capillaries may be expected to be less efficient. Trueta and his colleagues showed, further, that in the rabbit nervous stimuli can cause vasoconstriction of the arteries of the cortex above the juxtamedullary level, producing ischemia of the glomeruli and tubules of that portion of the cortex, and diversion of the blood through the juxtamedullary glomeruli into the vasa recta and thence into the venous system—the so-called "Trueta shunt." While the significance of this latter mechanism is not yet adequately understood in relation to the human renal circulation, the former anatomical vascular difference, which itself must affect the dynamics of the juxtamedullary glomerular circulation, is well established for the human kid-

ney. In the normal human kidney, therefore, the juxtamedullary glomeruli do differ significantly from the glomeruli elsewhere in the cortex at least in this manner; and the present study shows that they differ in their reaction to the injury that produces the obliterative glomerulosclerosis of lipoid nephrosis. The latter observation does not throw any light upon the nature of the injury responsible for the glomerular damage. However, the observation of such a striking difference in the susceptibility of the juxtamedullary glomeruli to the injurious process points up the need for more information regarding the structural and functional differences between the juxtamedullary glomeruli and the glomeruli elsewhere in the cortex. A more thorough understanding of those differences might, perhaps, provide a lead toward a better understanding of the pathogenesis of this obliterative glomerulosclerosis, the occurrence or non-occurrence of which determines whether a given patient with "pure lipoid nephrosis" will or will not develop fatal renal insufficiency.

SUMMARY

The glomeruli situated at the cortical-medullary junction of the kidney (the so-called juxtamedullary glomeruli) are strikingly more susceptible to the process which produces obliterative glomerulosclerosis in lipoid nephrosis than are the glomeruli in the other regions of the cortex. They are the first to be visibly altered by the sclerosing process, and the first to become obliterated by it. An adequate understanding of the pathogenesis of the glomerulosclerosis should account for this peculiar susceptibility of the juxtamedullary glomeruli to the injurious process responsible for the destructive glomerular damage; and a more detailed understanding of the normal differences between the juxtamedullary glomeruli and the other cortical glomeruli may be helpful toward the understanding of the at present obscure nature and mechanism of the process that produces the life-threatening glomerulosclerosis of lipoid nephrosis.

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EXPLANATION OF ILLUSTRATIONS

(Photomicrographs by Miss Patricia E. Whitney)

FIG. 1. Low power photomicrograph of section of a normal kidney. The area containing no glomeruli in the lower right portion of the picture is the medulla. The glomeruli in the lower zone of the cortex near the medulla are the juxtamedullary glomeruli.

FIG. 2. Glomerulus from an early case of pure lipoid nephrosis (Autopsy 12176). The arrow points to a thickened capillary basement membrane. It required meticulous examination of many glomeruli to find occasional thickened membranes such as this.

FIG. 3. Glomerulus from a case of pure lipoid nephrosis (Autopsy 15743), showing more extensive focal thickening of capillary basement membranes (arrows).

FIG. 4. Glomerulus from a case of pure lipoid nephrosis with obliterated glomeruli (see Figs. 7, 8, 9) confined to the juxtamedullary zone (Autopsy 25575), showing early focal deposition of hyaline in left hand portion of the tuft.

FIG. 5. Glomerulus from the juxtamedullary zone of a case of lipoid nephrosis (Autopsy 17845), showing a more advanced and diffuse deposition of hyaline in the tuft than in Fig. 4.

FIGS. 6, 7, 8 and 9. Glomeruli from a case of lipoid nephrosis (Autopsy 25575) in which obliterated glomeruli (Figs. 7, 8 9) were confined to the juxtamedullary zone. Fig. 6 shows normal glomeruli in the cortex above the juxtamedullary zone.

FIGS. 10 and 11. Glomeruli from a case of lipoid nephrosis (Autopsy 17845) in which obliterated glomeruli (Fig. 11) were confined to the juxtamedullary zone. Fig. 10 shows normal glomeruli in the cortex above the juxtamedullary zone.

FIG. 12. Glomerulus from a case (Autopsy 23124) that began as pure lipoid nephrosis and progressed to hypertension, renal insufficiency and death in uremia. There were obliterative glomerular lesions throughout the cortex. The picture shows two completely obliterated glomeruli in the subcapsular region of the cortex, adjacent to a glomerulus with no alteration other than focal thickening of capillary basement membranes. This illustrates that the glomerular lesions are by no means uniform, even in any given zone of the cortex.

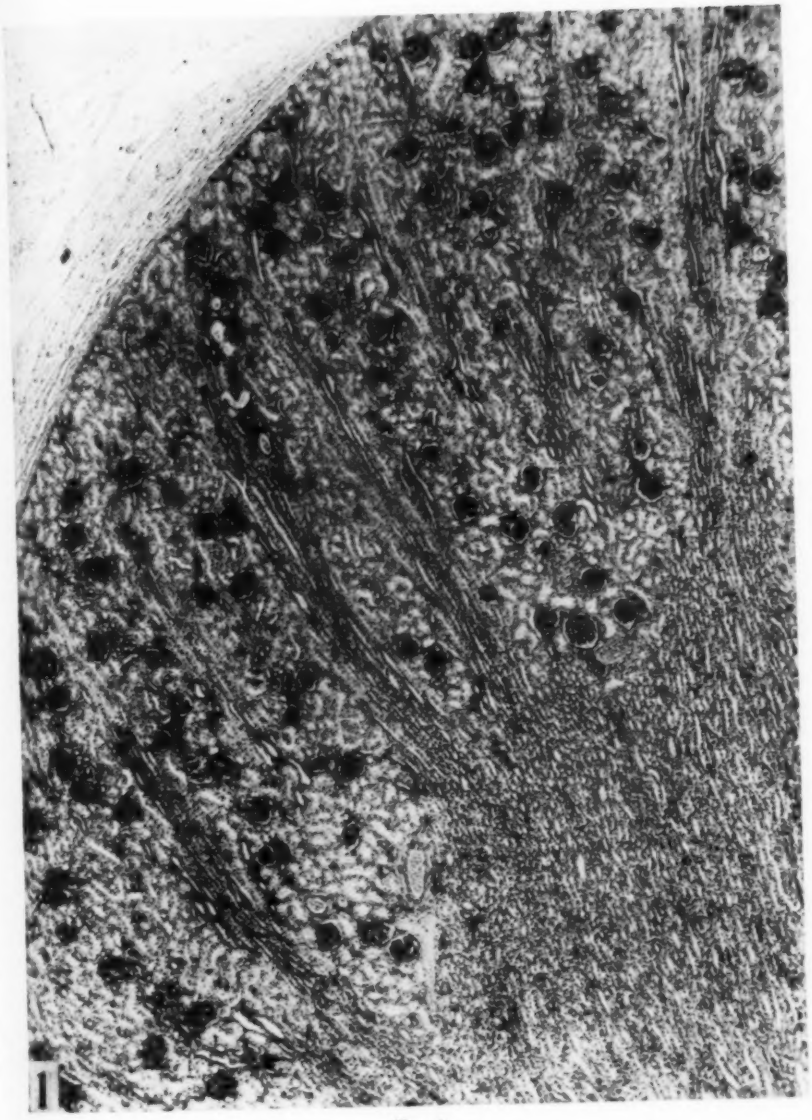
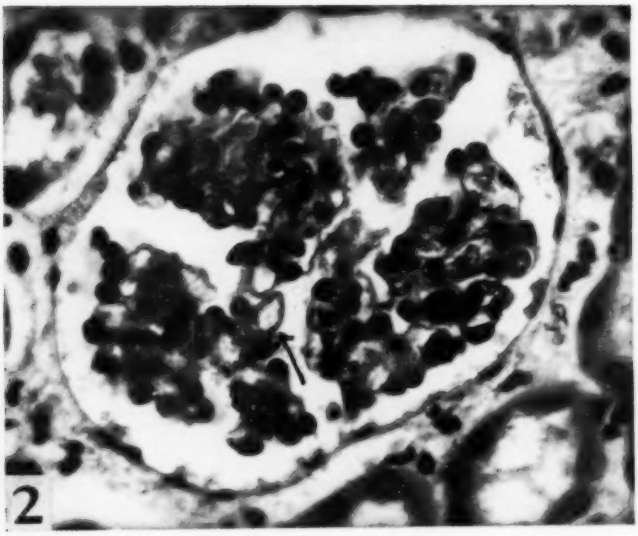


FIG. 1



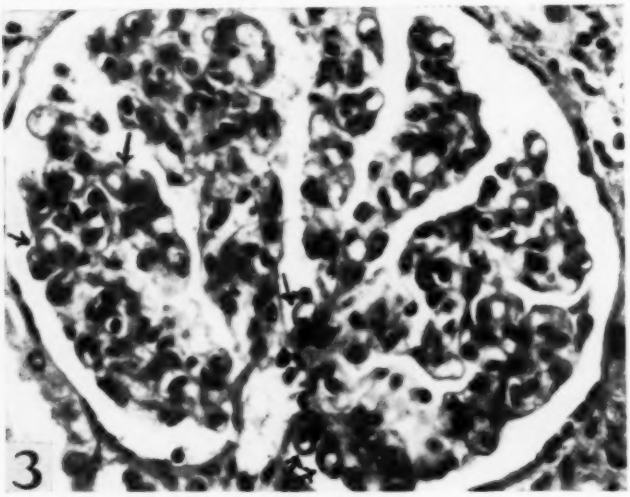
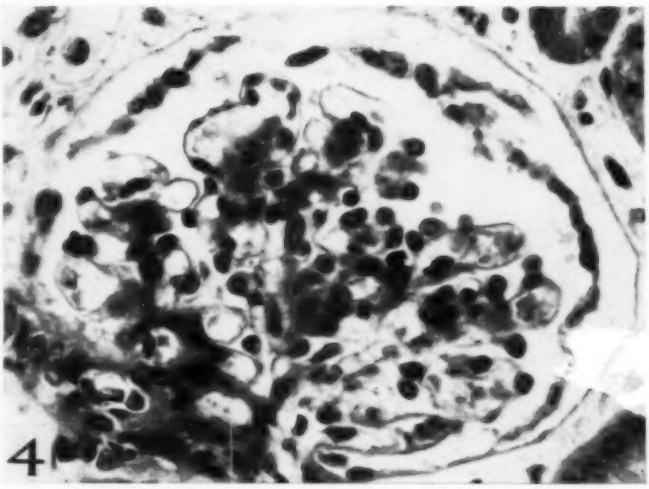


FIG. 2–3



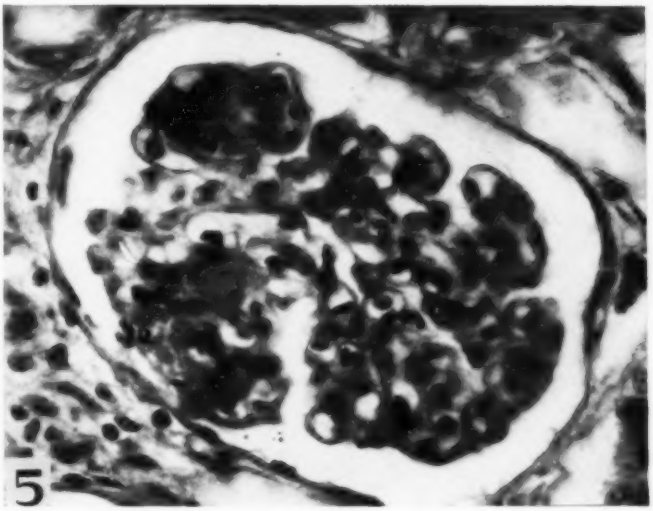
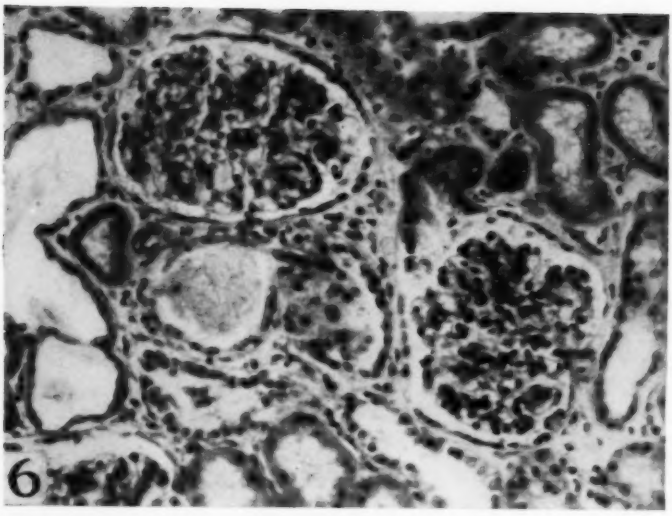


FIG. 4–5



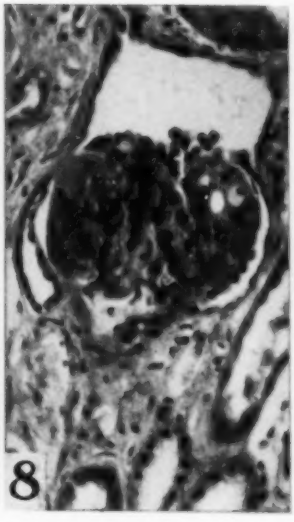
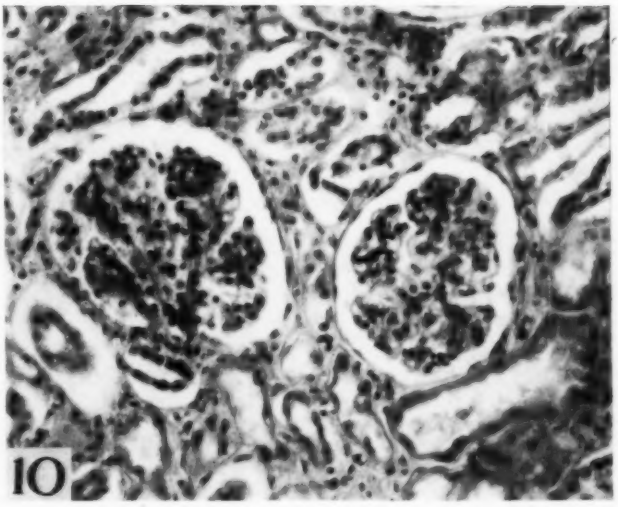


FIG. 6-9



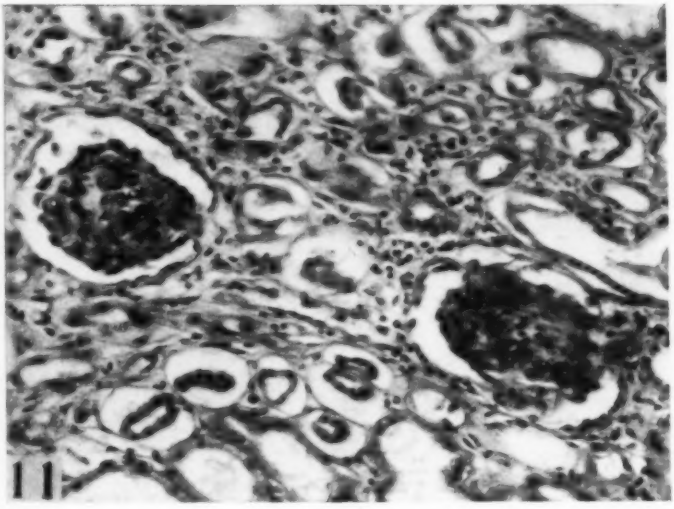


FIG. 10–11

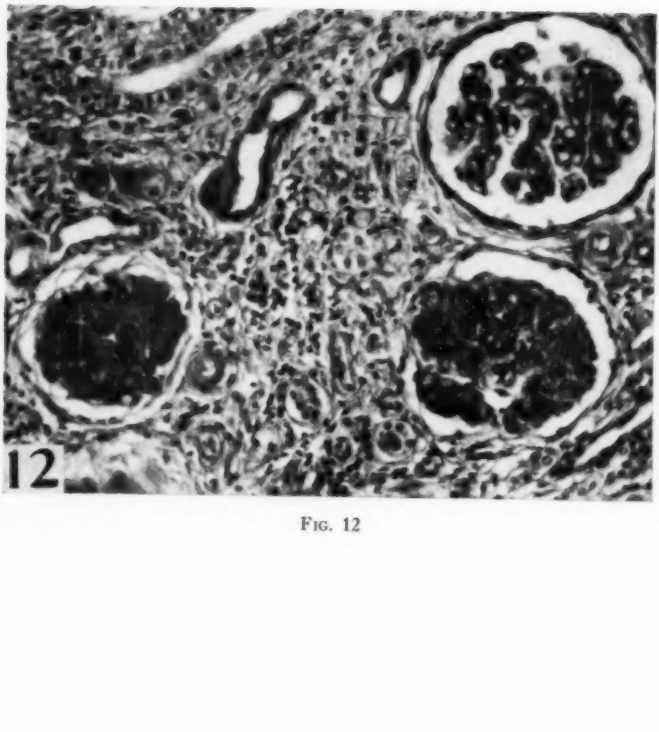


FIG. 12

ABSTRACTS OF PAPERS PRESENTED BEFORE THE MEETING OF THE JOHNS HOPKINS MEDICAL SOCIETY

January 14, 1957

STUDIES OF IMMUNOLOGIC MECHANISMS IN HYPERSENSITIVITY: ANAPHYLACTIC SHOCK INDUCED IN NORMAL GUINEA PIGS BY ANTIGEN-ANTIBODY COMPLEXES PREPARED IN VITRO

FREDERICK G. GERMUTH, JR. AND GEORGE E. MCKINNON

The allergic lesions of protracted anaphylaxis develop at a time when antibody forming in the tissues is undergoing rapid combination with excess antigen present in the surrounding fluid and circulating plasma. In previous studies, it has been suggested that antibody may be transported to the tissues in the form of soluble antigen-antibody complexes. The present study was undertaken to determine the role, if any, of soluble antigen-antibody complexes in the pathogenesis of allergy. The results show that supernatant fluids from antibody-excess antigen mixtures prepared *in vitro* are capable of eliciting symptoms characteristic of anaphylactic shock in normal unsensitized guinea pigs. The evidence strongly indicates that the active material is the soluble antigen-antibody complex. First, but for minor exceptions, only supernates from antigen-antibody mixtures prepared in antigen excess are capable of eliciting shock. Second, shock can be produced by mixtures of purified antibody (gamma globulin) and excess antigen. Third, the further addition of excess antibody to supernates originally prepared in antigen excess removes their anaphylactigenic properties. Fourth, soluble antigen-antibody complexes, prepared by the dissociation of washed immune precipitates by alkali or by mechanical agitation in the presence of additional antigen, are capable of producing shock. Finally, the amount of antibody contained in soluble antigen-antibody complexes capable of producing shock is similar to the amount required in passive anaphylaxis produced by the simultaneous injection of antigen and antibody.

THE COURSE AND PROGNOSIS OF THE RETICULOENDOTHELIOSES WITH PARTICULAR EMPHASIS ON SCHÜLLER-CHRISTIAN DISEASE

HARRIET G. GUILD, MARY E. AVERY AND J. G. MCAFEE

SUMMARY

1. Forty patients with reticuloendotheliosis seen at the Johns Hopkins Hospital are presented. These are classified as Letterer-Siwe disease, Schüller-Christian disease, and eosinophilic granuloma on the basis of the number and extent of the lesions, and their histological appearance. The duration of follow-up covers varying periods up to forty-three years.

2. There were twenty-four males and sixteen females in this series. Thirty-seven of the forty patients were white and three were colored.

3. Letterer-Siwe disease occurred in infants only. Schüller-Christian disease was most common in the first five years of life, but was seen at all ages up to forty-six years. Eosinophilic granuloma, although more common in the younger group, occurred in one patient at the age of sixty-one years.

4. There were two patients with Letterer-Siwe disease, in both of whom the disease was

fatal. There were twenty-nine patients with Schüller-Christian disease with only four fatalities. The nine patients with eosinophilic granuloma all recovered.

5. The emphasis of this report is on the group of patients with Schüller-Christian disease. Membranous bone defects, exophthalmos, and diabetes insipidus (the classical triad), while individually among the most common manifestations, were present in combination in only three patients. Other less familiar features of the disease are discussed. Of special interest is the range of diagnostic possibilities suggested by the presenting complaints. The radiological findings, particularly with reference to the skeleton, supplied the only helpful laboratory aid. There were no consistent abnormalities on chemical analysis of the blood; all serum cholesterol determinations were normal. Anemia was rare, and when it was present, was associated with a grave prognosis. Eosinophilia in the peripheral blood was notably absent. Disturbances in growth occurred in a few patients in whom there was other evidence of pituitary dysfunction. Of the twenty-nine patients, approximately one-third have recovered; about one-half, when last seen, still showed evidence of active disease; only one-seventh have died, giving a mortality of fourteen per cent.

6. In the nine patients with eosinophilic granuloma, lesions occurred mostly in the bones of the head and the pelvis, although in no two was the same area involved.

7. X-ray and steroid therapy have been useful in suppressing the lesions of Schüller-Christian disease. The isolated skeletal lesions of eosinophilic granuloma have responded to irradiation, and to curettage or excision.

8. With regression of the disease, bone and soft tissue lesions heal completely. When, however, diabetes insipidus results from infiltration of the pituitary stalk and deafness, from destruction of the inner ear occurring in lesions of the petrous-mastoid portions of the skull, these remain as permanent sequelae. In this series, pulmonary infiltrations also cleared completely, although there are rare case reports (in the literature) of resultant bronchiectasis.

9. The fact that the prognosis in Schüller-Christian disease is so much better than is generally realized justifies this report, as does the multiplicity of presenting complaints (such as chronic otitis media, gum lesions, certain skin manifestations, etc.) which do not immediately in themselves suggest the diagnosis.

COEXISTING TESTICULAR DEFICIENCY AND HYPERTHYROIDISM—BY DESIGN OR BY CHANCE

SAMUEL P. ASPER, JR. AND E. HUNTER WILSON, JR.

Coexisting functional abnormalities of various endocrine organs have been noted previously. In some instances such associations occur by chance, in others there exist mechanisms which may produce a second endocrinopathy in a patient already suffering an endocrine disorder. This report presents six patients with testicular deficiency of presumed long standing who developed hyperthyroidism. Whether this occurs by design or by chance is not known.

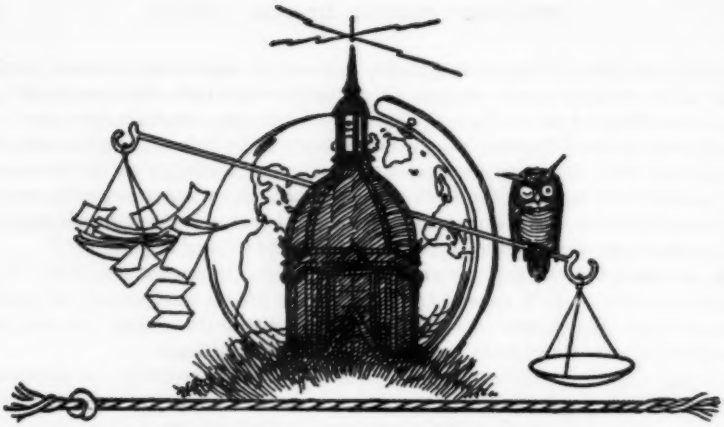
The six patients, whose ages varied between 32 and 67 years, had typical manifestations of hyperthyroidism. They had shown response to treatment. In addition, each had been married for many years and their marriages were infertile, although two wives had children by other consorts. Two patients had severe mumps orchitis after puberty. All had aspermia and all but one patient had testicular atrophy. Four of the six patients had had gynecomastia for many years.

Histological examination of the testes showed a somewhat variable pattern, but in most

there was hyalinization of the tubules, slightly increased thickness of the basement membrane of the tubules or slight tubular sclerosis, abundant interstitial cells with some clumping and an arrest or failure of spermatogenesis. The testicular atrophy resembles that seen in some patients with pseudo-Klinefelter's syndrome as described by Nelson (Acta Endocrinologica **23:** 227–245, 1956). Moreover, the chromosomal sex pattern studied in four of the six patients was male; whereas in true-Klinefelter's syndrome there appears to be a genetic female sex chromosomal pattern. Excretion of follicle stimulating hormone in the urine was measured in three patients and was found to be normal in two and increased in one.

The records of 192 male patients with hyperthyroidism examined at The Johns Hopkins Hospital were reviewed. Of these 51 (26 per cent) had infertile marriages of two years duration or more. This incidence of infertility is higher than that recorded for the general population—usually stated to be about 10 per cent of all marriages.

Although there is experimental data to show that the thyrotropic and gonadotropic hormones are excreted by the same type of pituitary cell, there is no evidence at present to prove that excess thyrotropin excretion produced hyperthyroidism in these patients with testicular deficiency.



BOOK REVIEWS

Diseases of the Heart and Circulation, 2nd revised and enlarged edition. By PAUL WOOD. 1005 pp., $15.00. J. B. Lippincott Co., Philadelphia, Pa.

The first edition of Paul Wood's text was enthusiastically received on publication in 1950. Similar success is likely for the second edition which is a review of British cardiology at its best. The author has succeeded in his well phrased objective:

> I have attempted to maintain a proper balance between man and his instruments, between experienced opinion and statistics, between traditional views and the heterodox, between bedside medicine and special tests, between the practical and the academic, and so to link the past with the present.

New and incompletely developed or evaluated techniques are not mentioned merely out of fear of incompleteness. Electrocardiograms are mounted in reference to the Einthoven triangle, with each unipolar limb lead at the appropriate apex, each standard limb lead along the appropriate side and the six precordials across the middle. The section on neurocirculatory asthenia—or as Wood, who has investigated the condition personably, prefers, Da Costa's syndrome—is excellent. A copy of the life-size portrait by Ian Tillard is presented and provides an unforgettable picture of the characteristic appearance of patients suffering from this condition. The book is well illustrated and printed, and is supplied with key references to the literature. Full titles of articles and monographs are provided. The book reflects the admirable ability of so many British physicians to milk a maximum of information out of the history and physical examination. Heaves, pulses, auscultatory signs are gone into in detail and illustrated with graphic records such as phonocardiograms of Aubrey Leatham and others. In describing the pulse, terms unfamiliar to us but probably useful, such as percussion wave and tidal wave, are used. Some rather surprising statements are made: In thyrotoxicosis and in complete heart block a diastolic apical murmur may be heard, presumably due to "torrential" mitral flow (p. 68). The use of "torrential" in this connection originated, I believe, with Wood. A mitral diastolic murmur was found in 33% of Wood's cases of coarctation of the aorta, even after cases of ventricular septal defect and patent ductus arteriosus were excluded! Associated fibroelastosis was speculated about as a basis in some of these cases.

A few of the x-rays should be improved or left out. The characteristics of pericardial pain are not as fully described as would be desirable (p. 4). Dissecting aneurysm of the aorta is

classified with the traumatic lesions and more specifically with what the author terms, seemingly paradoxically, spontaneous traumatic lesions (p. 922). It takes a moment's thought to realize that what Wood means is that the trauma of the circulation itself is related to the development of dissecting aneurysm. Peripheral vascular disease is not discussed. It seems that 1-hydrazinophthalazine for the treatment of hypertension is dismissed in too summary a manner. The reviewer is irritated by the frequent reference (e.g., pp. 36, 344, 567) to "hypoplasia of the aorta" as characteristic of the Marfan syndrome and doubts that the person affected by this hereditary disorder has any increased susceptibility to rheumatic fever (p. 36). If a large American audience is desired abbreviations not used in this country (e.g., "t.d.s.", p. 303) should be avoided. Mitral incompetence, aortic incompetence, etc., etc., are inexact terms, since a stenotic value is also incompetent in the performance of one function of a valve. However, British cardiologists in general, not just Paul Wood, are guilty of this mis-usage. I would prefer to see *regurgitation* used. The author has been more impressed with mictine (p. 303) and less impressed with diamox (p. 309), as diuretic agents, than has the reviewer.

In general Wood's textbook is highly recommended.

VICTOR A. MCKUSICK

Dermatology. By DONALD M. PILLSBURY, WALTER B. SHELLEY and ALBERT M. KLIGMAN. 1331 pp., $20.00. W. B. Saunders Co., Philadelphia, Pa.

The authors of this new textbook are three of the most talented, industrious and imaginative physicians in their field. The senior author, Donald M. Pillsbury, is the distinguished head of the Philadelphia school where dermatology has flourished for almost a century. After a successful tour of military duty in World War II, during which he made many significant contributions, Pillsbury inherited the professorship of dermatology at the University of Pennsylvania from his former chief, Dr. John H. Stokes. Taking full advantage of a ripe opportunity he augmented his already strong and competent staff by gathering around him one of the most eager and talented groups of young physicians ever assembled in a department of dermatology. From this group emerged the co-authors, Walter Shelley and Albert Kligman, as well as several professors and department heads currently in other universities and clinics.

During the past ten years Pillsbury's group developed many new concepts in dermatology. In an atmosphere and setting designed for superior clinical and laboratory investigations many old undocumented notions were abandoned and some old undocumented theories were documented by modern methods. Much of the text is based on first hand clinical and investigative experience and therefore the book is vital and fresh. It is not primarily a review of the work of others.

The fundamental aspects of anatomy and physiology are magnificiently presented. Discussions of the methods of dermatologic diagnosis are extensive. Pathologic changes are not considered in detail, but the authors indicate those diseases in which a biopsy is helpful or essential. For diseases in which one or two methods of treatment are outstanding this is also stated. For those in which several treatment plans must sometimes be tried, the order of the authors' preference is given. "Where (in the opinion of the authors) it appears that no satisfactory method of treatment is available, it has seemed proper (for the authors) to say so frankly." The length of discussions of the clinical characteristics of the dermatologic syndromes was varied at will depending on emphasis the authors deemed necessary. The more common diseases are dealt with in detail. The exceedingly rare diseases are briefly described.

There are very few references. This is in contrast to the other great American textbooks of dermatology, all of which are detailed scholarly treatises presented in encyclopedic fashion

replete with literally thousands of references. In their preface the authors justify their viewpoint regarding lack of numerous references as follows:

"In any extensive text, the problem of inclusion of *pertinent references* is a difficult one and is never solved to everyone's satisfaction. Exhaustive and complete lists of references, of the type essential to monographs and review articles, are impractical in textbooks by reason of considerations of space. References in the body of the text are disconcerting and often meaningless to the non-specialist reader, and also offer difficulty in deciding whether the paper cited deserves merely a literary nod, a low bow or a complete genuflection. Moreover, lists of references too frequently include an overlarge proportion of the papers of the authors and their close colleagues; it is difficult to maintain adequate objectivity in such matters. We have, therefore, adopted the plan of including only one or a few key references to the subject matter of each chapter, and these should serve as an adequate starting point for the reader who desires to consult original sources. The discussions include a considerable number of unpublished studies from our own group, but no specific reference to these has seemed necessary."

MAURICE SULLIVAN

Textbook of Medical Physiology. By ARTHUR C. GUYTON. 1030 pp., $13.50. W. B. Saunders Co., Philadelphia, Pa.

In his preface the author states that perhaps the most important advantage of single authorship is that a perspective can be achieved "that can be more nearly that of the student who desperately needs all the aid that we can give him as he is being introduced to the complexities of body function." However the reviewers cannot recommend this text, even to desperate students. Not only does it contain more than a reasonable amount of formulations to which most authorities would take exception, but its general approach is unsound and misleading. In attempting to streamline the subject, Guyton has discounted the view that the nature of the evidence is important. This does not mean that students have to be submerged in experimental details or controversies, but some degree of technical basis for statements regarding bodily function is necessary. Without such a basis, one is headed back toward the Dark Ages. The compounding of experimental observations must not be taken as the excuse for the abnegation of the attempt to develop the students selective and critical faculties, for they were never so badly needed as they are at present.

Specifically, Guyton's treatment is qualitative, descriptive and dogmatic. The tendency to make statements without sufficient relationship to the type of experimental approach from which they have been derived, and by which they must be evaluated, is particularly evident in the treatment of kidney function. No trace of any historical development of the subject appears. It is stated that the fluid that filters through the glomerulus is known as the glomerular filtrate, but there is no explicit reference to the work of Richards and associates. Reabsorption is discussed in purely qualitative terms; active secretion is dismissed in two brief paragraphs as "of little importance physiologically", and the whole subject of reabsorption and secretion is presented without reference to the clearance techniques by which these functions can be evaluated. A figure for the rate of glomerular filtration is given without discussion of how the figure has been obtained, or what factors might modify its magnitude. Similarly figures for renal blood flow are given quite divorced from any indication as to the type of procedure by which they might have been obtained, or what their degree of reliability might be. Following several pages of this, the concept of plasma clearance is covered very summarily, with mention of the uses of inulin, PAH, etc., but the opportunity is entirely missed to develop the subject of kidney function logically in relation to the very considerable advances of the last thirty years. Following this, there are 15 pages devoted to "the physi-

ology of kidney disease". A total of 66 pages are devoted to body fluids and the kidney, which should have been sufficient space to permit a rational approach.

The second chapter, headed "the internal environment and the philosophy of its control", contained the following: "The electroyltes Na, Ca . . . are present in very large quantities in extracellular fluids" (no figure given). It is stated that because of the law of mass action, the accumulation of waste products would stop metabolic reactions if such accumulation were allowed to continue. This type of statement is well adapted to lull young minds to sleep regarding reaction rate control. "The fluid pressure in the arterial end of the capillary causes fluid to *leak* from the capillary into the tissue spaces, and *at the venous end of the capillary the proteins of the blood create osmotic pressure* which pulls fluid into the capillary." . . . "Excess carbon dioxide released into the extracellular fluids by the active cells of the body *flows with the extracellular fluid* to the respiratory center."

Chapters 3 and 4 present current theories of nerve resting and action potentials, and the action of acetylcholine, as if they were the ultimate truth. From the text, one gets no feeling of the intellectual adventure of an exciting and rapidly growing field, in which theories are used as more or less satisfactory schema which may bear some resemblance to reality. In place of any such seductive distractions nearly everything is fully explained. There are no distressing uncertainties.

In Chapter 6, on cardiac muscle and its rhythmic contractions, the author again neglects both the historical perspective as well as the recent advances in the field. Figure 53, illustrating the relationship between cardiac membrane potential and cardiac contractions, is an extremely poor and misleading one because it does not correspond accurately to the events occurring in any one region of the heart. At the present time there are many excellent photographic records available from actual experiments showing the simultaneous registration of the electrical and mechanical events in the heart. This figure, 53, would lead the student to believe that the electrical events are everywhere exactly the same in all parts of the heart, and furthermore that they are always similarly related to the mechanical events. On page 68, he speaks of the excitability being *fatigued*. This is a most unfortunate and inaccurate description of the state of excitability under these conditions. In addition, we are not aware of any evidence for the statement that when ventricular muscle beats rapidly its excitability is depressed. In Chapter 23, p. 294, he says that the refractory period of ventricular muscle at the base of the heart is longer than the refractory period near the apex, although no experimental evidence is cited for this statement. As far as we know, none exists.

The chapters on blood pressure and flow, the cardiac output and the ECG are, in general, fairly well done. Although the word *explain* is used where *describe* would be more enlightening, sections which are simply descriptive, such as the one on endocrinology, are among the more satisfactory, except for a fair number of errors. Tri-iodothyronine is not mentioned. An excessive amount of clinical opinion is expressed throughout, which is out of place in a book which attempts to be introductory on as simple a basis as possible: nevertheless, the use of cortisone to control the adrenogenital syndrome is not mentioned, although this is an effect of considerable interest, both theoretically and practically. On the contrary the statement is made that "thus far no specific inhibiting drug has been found to block secretion by the adrenal gland. Consequently the only treatment at present is surgical removal of the adrenal tumor or hyperplastic gland."

Overall, the book is superficial, full of incorrect generalizations, and potentially harmful to the beginning student for whom it was intended. In attempting to write down to the level of medical students, Guyton has seriously underestimated both their capacities and their needs.

EVELYN HOWARD and JEAN MARSHALL

Sick Children. Diagnosis and Treatment, 7th edition. By DONALD PATERSON. Revised by REGINALD LIGHTWOOD with the assistance of F. S. W. BRIMBLECOMBE. 395 pp., $8.75. J. B. Lippincott Co., Philadelphia, Pa.

To present a worthwhile condensation of such a broad subject as "sick children" their diagnosis and treatment, is a challenging and difficult task. Dr. Paterson has tackled this task with a moderately successful result.

A very readable brief review of general pediatrics is presented with the emphasis on diagnosis and treatment. The chapters on vitamin deficiencies, tuberculosis, rheumatic fever and tropical disease are excellent and the presentation of childhood neurological illness (J. P. M. Tizard) is well organized.

Several subjects, however, are poorly covered: abnormal hemoglobin states are barely mentioned, the differential diagnosis of neonatal icterus is incomplete and poisonings receive very little mention. Some of the newer infectious diseases such as cytometalic inclusion disease, cat scratch fever, and interstitial plasma cell pneumonia are not even mentioned. Furthermore certain recent advances have not been included. For example while discussing the adrenogenital syndrome the statement "treatment with cortisone . . . is still in the experimental stage and no conclusion can yet be drawn" is made. Recent publications attest to the inaccuracy of this statement. The newer diagnostic methods of sweat analysis in fibro-cystic disease of the pancreas are not mentioned nor is potassium therapy in the treatment of congenital pyloric stenosis.

However, the content is generally complete and the pleasant English style of presentation adds to the readability. Phraseology such as "the rickety child has the head of a philosopher, the chest of a greyhound, the legs of a grand piano and the tummy of a poisoned pup" abound and such make for enjoyable relaxing reading.

This book then is recommended as an excellent source for the highlights of the majority of the common pediatric diseases. It is brief. By its very nature, it needs be brief but does contain much valuable information and many enjoyable witticisms.

GERALD H. HOLMAN

Hormones and the Aging Process. Edited by EARL T. ENGLE and GREGORY PINCUS. 323 pp., $8.50. Academic Press, New York, N. Y.

This volume consists of the proceedings of a conference held in 1955, and should be valuable for purposes of orientation in contemporary thinking on matters pertaining to the endocrinology of aging. There are 18 papers, with records of discussions. The papers are generally to the point and directed to the general professional reader rather than to the specialist. The editors state that they recognize that "a comprehensive survey of our knowledge in this field is not attained, nor indeed has it been sought. Rather it is our aim to present modern experimentation as it is functioning operationally. . . . Certainly experimentation in this difficult and too neglected field has far from reached its climax, and if these chapters act as stimulants to obviously needed investigation, we shall be happy."

For those hormones susceptible of quantitative analysis, accounts are presented of the variations with advancing age by G. Pincus and by L. T. Samuels, and by A. Albert. R. W. Rawson discusses the thyroid in aging. Some papers are concerned with the role of hormones in the tissue wasting and osteoporosis characteristic of aged individuals. There are a number of papers describing recent data on experimental steroid medication in heart disease, osteoporosis, and cancer as well as the use of such medication in senile individuals without specific disease.

The book deserves to be widely read.

EVELYN HOWARD

BOOKS RECEIVED FOR REVIEW

Allergic Dermatoses. Edited by RUDOLF L. BAER. 110 pp., $3.00. J. B. Lippincott Co., Philadelphia, Pa.

Bladder Tumors. A Symposium. Prepared under the auspices of the American Cancer Society. 92 pp., $4.00. J. B. Lippincott Co., Philadelphia, Pa.

Enzyme Antigen and Virus. A Study of Macromolecular Pattern in Action. By SIR MACFARLANE BURNET. 193 pp., $3.50. Cambridge University Press, New York, N. Y.

Fundamentals of Clinical Fluoroscopy, 2nd edition, revised and enlarged. By CHARLES B. STORCH. 305 pp., $8.75. Grune & Stratton, New York, N. Y.

Liver: Structure and Function. By HANS POPPER and FENTON SCHAFFNER. 777 pp., $20.00. McGraw-Hill Book Co., New York, N. Y.

Out of the Test Tube: The Story of Chemistry, 5th edition, revised and expanded. By HARRY N. HOLMES. 313 pp., $4.50. Emerson Books, New York, N. Y.

Pregnancy and Birth. A Book for Expectant Parents. By ALAN F. GUTTMACHER. 335 pp., $4.50. The Viking Press, New York, N. Y.

Problems of Aging. A collection of papers presented at The Annual Graduate Fortnight (October, 1955) of The New York Academy of Medicine. 240 pp., $3.50. From the Bulletin of The New York Academy of Medicine. Distributed by George Eliot, Medical and Scientific Books, New York, N. Y.